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THE UNIVERSITY OF ALBERTA

THE TOTAL SYNTHESIS OF METHYMYCIN

by

© GORDON STEVEN BATES

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF

DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY
EDMONTON, ALBERTA

SPRING, 1976

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled

"THE TOTAL SYNTHESIS OF METHYMYCIN"

submitted by GORDON STEVEN BATES in partial fulfilment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

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Date ... March 22 1976 ...

TO FRANCES, MY WIFE, LOVER,
FRIEND, AND FELLOW CHEMIST

ABSTRACT

Organic chemists in the past have explored the area of natural product chemistry so extensively that general approaches for syntheses of most of the important groups of compounds, including steroids, terpenes and alkaloids, are available. In the field of antibiotics, total syntheses of penicillins and cephalosporins, and tetracyclins were already completed, and the only remaining major family of antibiotics which presented a challenge to synthetic organic chemists was the macrolides. These compounds consist of a medium or large lactone containing a complex array of ketonic and hydroxy functions along with glycosidically-bound deoxy sugars.

This thesis describes the total synthesis of methymycin 12, the smallest macrolide and the first member of this family of antibiotics to be successfully synthesized. Our approach to this synthesis was based on a conformational analysis of the system, and involved the cyclization of the appropriately substituted aliphatic hydroxy thiol ester 139. This lactone precursor was prepared by condensing two fragments; one segment containing the C_1 through C_7 centres of the lactone, and the other consisting of the remaining C_8 through C_{13} portion. A successful, efficient synthesis of the former fragment, the racemic form of the Djerassi-Prelog lactonic acid 6, has been accomplished starting with

bicyclo[4.2.1]nona-2,4,6-triene 69, a pyrolysis product of the $[_{\pi}2_{s} + {}_{\pi}2_{s}]$ dimers of norbornadiene. This lactonic acid is a degradation product of the macrolide antibiotics methymycin, neomethymycin, pikromycin and narbomycin, and contains all of the stereochemical features present in the C_1-C_7 portion of 12. The other fragment of the lactone precursor, epoxy aldehyde (+)-103, was synthesized by conventional methods. An efficient cyclization of 139 to give the methymycin aglycone, methynolide, with the aid of a mercury(II) salt, a reagent developed specifically for this purpose, followed by removal of a hydroxy-protecting silyl ether, gave gratifying yields of methynolide 14.

The difficult task of glycosylation of the synthetic methynolide was achieved by reacting the aglycone with 1-α-bromo-2-acetoxydesosamine hydrobromide 154, followed by hydrolysis of the 2'-acetoxy group to give a 5:1 mixture of methymycin (β-glycoside) and *epi*-methymycin (α-glycoside) in a 25% yield based on methynolide. These synthetic antibiotics showed 100% and 20% microbiological activity, respectively, against *Steptococcus pyrogenes* group A, type 5.

During the synthesis of methymycin, it became necessary to convert an alcohol (or halide) into the corresponding hydrocarbon. A hydride-containing cuprate reagent, developed for this purpose, was found to readily reduce halides and sulphonate esters cleanly and in high yields. We also required a reagent capable of introducing a thiol ester function in a selective manner, and found that primary, secondary and tertiary thiol esters could be formed in excellent yields by reaction of the corresponding thallium(I) thiolate with a carboxylic phosphoric anhydride (or carboxylic acid chloride).

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TABLE OF CONTENTS

Page

ABSTRACT . . . . v.

ACKNOWLEDGEMENTS . . . . viii.

LIST OF TABLES . . . . xi.

LIST OF FIGURES . . . . xii.

PART I: THE MACROLIDE ANTIBIOTICS

1. INTRODUCTION 1
   - A) STRUCTURE 1
   - B) BIOLOGICAL ACTIVITY 13
   - C) BIOGENESIS OF MACROLIDES 20
   - D) A CONFIGURATIONAL MODEL FOR MACROLIDES . . 30
   - E) CONFORMATIONAL ANALYSIS OF MACROLIDE AGYLCONES. 38
2. PROPERTIES AND CONSTITUTION OF METHYMYCIN. . . 46
3. PREVIOUS SYNTHETIC STUDIES OF MACROLIDES . . . 61
4. A SYNTHETIC APPROACH TOWARDS METHYMYCIN. . . . 73
5. A SYNTHESIS OF THE RACEMIC DJERASSI-PRELOG LACTONIC ACID. 81
6. THE LEFT HAND SIDE OF METHYNOLIDE. 108
7. COMPLETION OF THE SYNTHESIS OF METHYMYCIN. . . 116
   - A) SYNTHESIS OF METHYNOLIDE 116
   - B) CONVERSION OF METHYNOLIDE INTO METHYMYCIN 135
8. EXPERIMENTAL 142

Page

PART II: NEW REAGENTS FOR ORGANIC SYNTHESIS

1. A GENERAL SELECTIVE SYNTHESIS OF THIOL ESTERS 222

2. NEW ORGANOCUPRATE REAGENTS 229

   A) INTRODUCTION 229

   B) HYDRIDE-CONTAINING ORGANOCUPRATES 243

3. EXPERIMENTAL 262

REFERENCES 273

LIST OF TABLES

Table Page

1 Macrolide Antibiotics 9

2 *In Vitro* Inhibitory Concentrations of Different Macrolide Antibiotics 13

3 Chirality of Methymycin 60

4 Lactonization of ω-Hydroxy Carboxylic Acids 69

5 Effect of $Eu(fod)_3$ on the Chemical Shifts of the Bridging Protons in **74** and **76** 91

6 Chemical Shifts of the Methyl Signals in (±)-**25** and (+)-**25** 105

7 Pmr Analysis of (±)-**6** 106

8 Cmr Analysis of (±)-**6** 107

9 Reaction of Hg(II) and Tl(III) with *S*-*tert*-Butyl Cyclohexanemethanethioate (**140**) and Alcohols 131

10 Examples of the Thiol Ester Synthesis 225

11 Reduction with Reagent I 246

12 Deuterium Incorporation into Norbornane 251

13 Reduction of 2-Bromononane with LiCuHR 254

14 Reduction with 4 Molar Equivalents of $LiCuH(\textit{n}-C_4H_9)$ in Ether at 25° 257

LIST OF FIGURES

Figure		Page
1	The Macrolide Lactones	3
2	The Macrolide Sugars	6
3	Protein Synthesis	16
4	Fatty Acid Biosynthesis	22
5	Biosynthesis of Macrolide Sugars	28
6	Celmer's Model for Macrolide Stereochemistry	36
7	Conformation of Erythronolide B	42
8	Russian Attempt at Synthesis of (±)-6	55
9	Possible Reaction Mechanisms of Organocuprates with Alkyl Halides	239
10	Approximate Rates of Reduction of 2-Bromononane with $LiCuH(n-C_4H_9)$ at Various Temperatures	256

PART I: THE MACROLIDE ANTIBIOTICS

CHAPTER 1: INTRODUCTION

A) STRUCTURE

Soil microorganisms have been recognized as sources of novel chemical entities for many decades. Many of these substances have the property of inhibiting the growth of bacteria and/or fungi, and are known as antibiotics.[1]

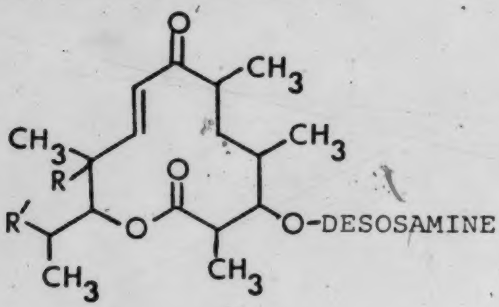
In 1950 Brockmann and Henkel[2] reported the isolation of a biologically active, basic compound from an unidentified Streptomyces organism obtained from a soil sample. This new substance was named pikromycin on account of its bitter taste. The general chemical behaviour of this new compound indicated that it was different from any class of antibiotics known at that time. By 1956 Streptomyces had yielded other compounds (*e.g.* methymycin, erythromycin) whose chemical behaviour indicated that they were closely related to pikromycin. Woodward[3] proposed the family name "macrolide" for these antibiotics since it had been established that carbomycin (magnamycin),[3] methymycin,[4] pikromycin[5] and erythromycin[6] contained a lactone incorporated in a medium- or large-ring system.

Because a large number of lactonic natural products have since been obtained, Woodward's original definition has been modified and is now used in a more restricted sense. The group of substances bearing a close resemblance to pikromycin, which have a large lactone containing various ketonic and hydroxy functions along with glycosidically-bound deoxy sugars, are referred to as nonpolyene macrolides, or more simply just macrolides. Reference is made to several macrolides in this thesis. Their structures are represented collectively in Figure 1. The deoxy sugars found in the macrolides were the first distinguishing chemical feature of this class of compounds. These sugars, with the exception of oleandrose,[7] have not been isolated from other classes of natural products, and the presence of one of these sugars is often the first indication that a newly isolated antibiotic is a member of the macrolide family. Definitive structures for some of these sugars are shown in Figure 2.

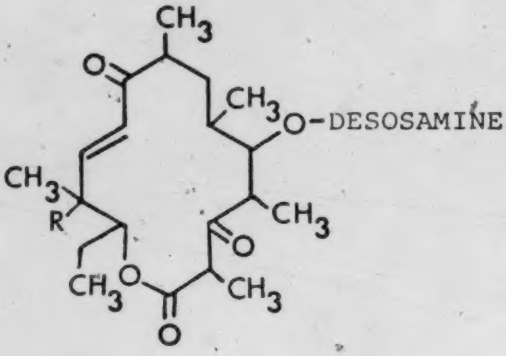
A second group of compounds presumably included in Woodward's original definition have extended conjugated double bond systems in addition to the features of the macrolides and are termed polyene macrolides. All other remaining compounds (e.g. nonactin, prenophorin, vermiculin) are referred to as pseudomacrolides. These compounds do not generally contain sugar moieties. An example of each of these latter two classes of compound is given in Figure 1.

Figure 1: The Macrolide Lactones

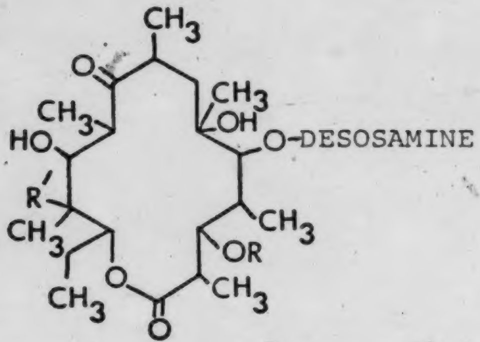
(Nonpolyene) Macrolides


O
CH3
CH3
CH3
R
R'
O
O
O-DESOSAMINE
CH3
CH3

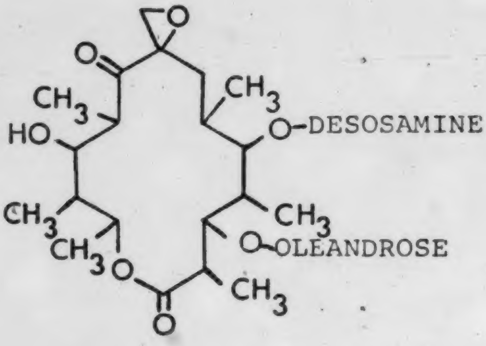
	R	R'
Methymycin	OH	H
Neomethymycin	H	OH


CH3
O
CH3
O-DESOSAMINE
CH3
R
CH3
O
CH3
O
CH3
O

	R
Pikromycin	OH
Narbomycin	H


CH3
O
CH3
CH3
OH
HO
O-DESOSAMINE
R'
CH3
CH3
OR
CH3
O
CH3
O

	R	R'
Erythromycin A	cladinose	OH
Erythromycin B	cladinose	H
Erythromycin C	mycarose	OH


O
O
CH3
CH3
HO
O-DESOSAMINE
CH3
CH3
O-OLEANDROSE
CH3
O
CH3
O

Oleandomycin

Leucomycins

	R	R'
A_1	H	isovaleryl
A_3	acetyl	isovaleryl
A_4	acetyl	n-butyryl
A_5	H	n-butyryl
A_6	acetyl	propionyl
A_7	H	propionyl
A_8	acetyl	acetyl
A_9	H	acetyl

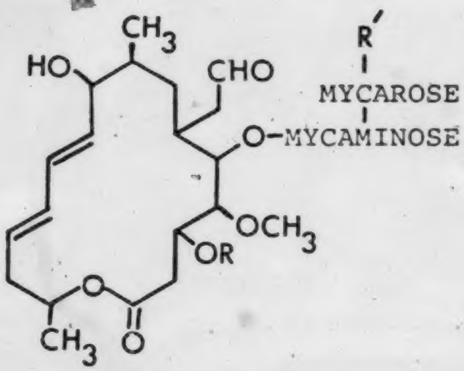
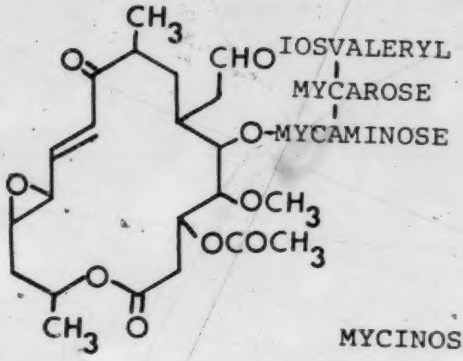
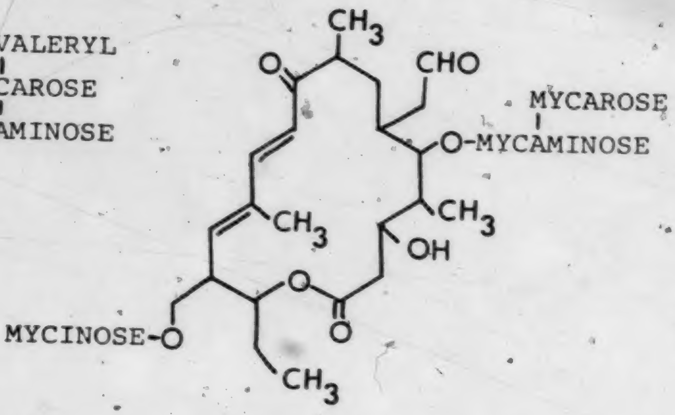

HO
CH3
CHO
R'
MYCAROSE
O-MYCAMINOSE
OCH3
OR
O
CH3
O

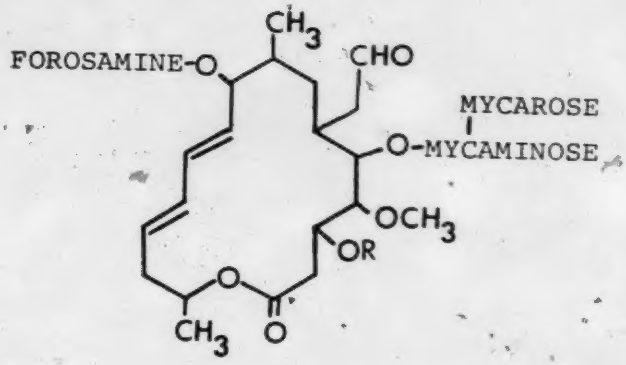
Figure 1 (continued)


CH3
CHO
IOSVALERYL
MYCAROSE
O-MYCAMINOSE
OCH3
OCOCH3
CH3
O

Carbomycin A (Magnamycin A)


CH3
CHO
MYCAROSE
O-MYCAMINOSE
CH3
CH3
OH
MYCINOSE-O
O
CH3

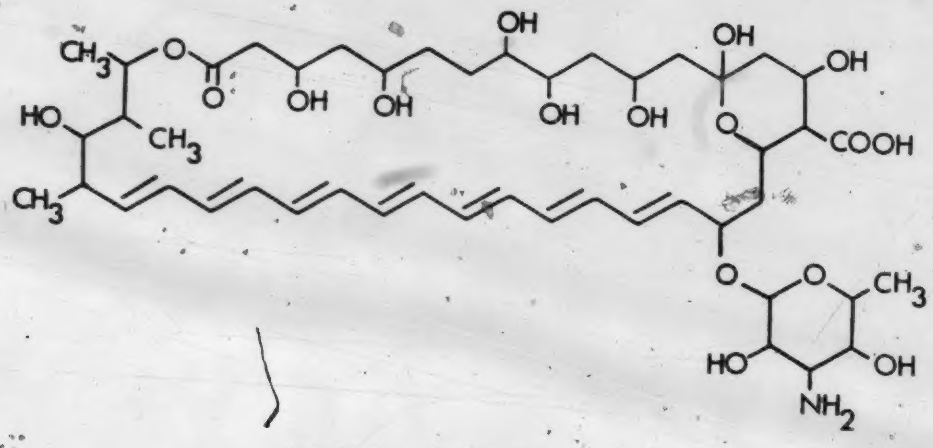
Tylosin


CH3
FOROSAMINE-O
CHO
MYCAROSE
O-MYCAMINOSE
OCH3
OR
CH3
O

	R
Spiramycin I	H
Spiramycin II	acetyl
Spiramycin III	propionyl

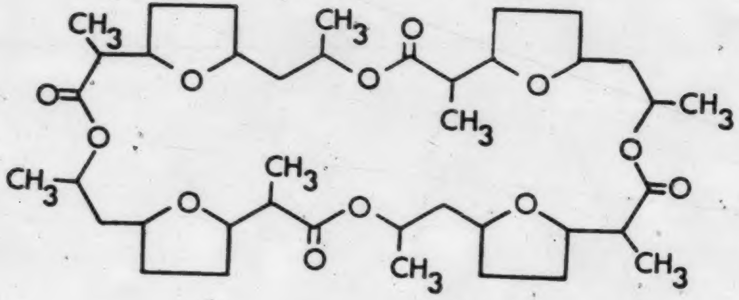
Figure 1 (continued)

Polyene Macrolides



Amphotericin B

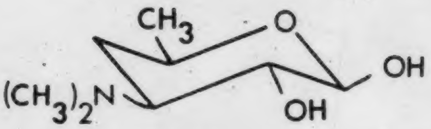
Pseudomacrolides



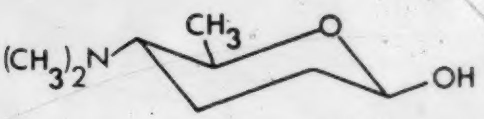
Nonactin

Figure 2: The Macrolide Sugars

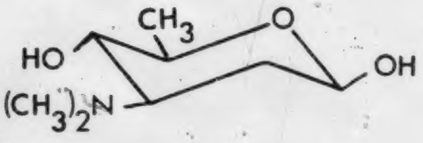
D-SUGARS


CH3
O
OH
(CH3)2N
OH

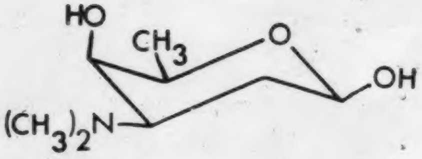
D-Desosamine


CH3
O
(CH3)2N
OH

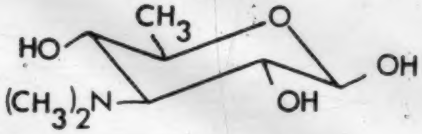
D-Forosamine


CH3
O
HO
OH
(CH3)2N

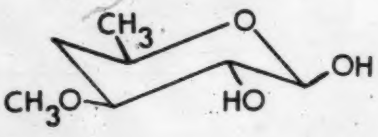
D-Angolosamine


HO
CH3
O
OH
(CH3)2N

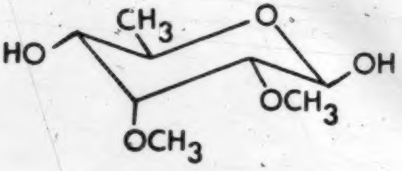
D-Rhodosamine


CH3
O
HO
OH
(CH3)2N
OH

D-Mycaminose


CH3
O
OH
CH3O
HO

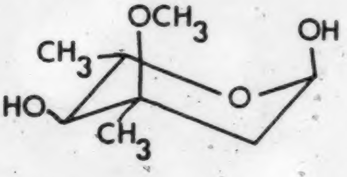
D-Chalcose


CH3
O
HO
OH
OCH3
OCH3

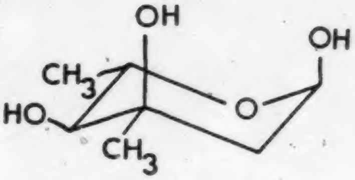
D-Mycinose

Figure 2 (continued)

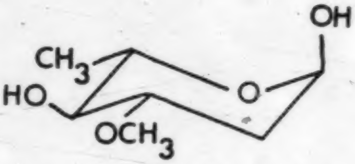
L-Sugars



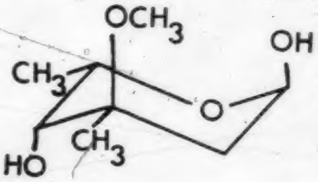
L-Cladinose



L-Mycarose



L-Oleandrose



L-Arcanose

Even with this restricted classification there are a great many representatives of the macrolide family. These are often a number of closely related compounds within a single group, and thus the complete list is much longer than indicated in Table 1. For instance, there are nine known leucomycins and three spiramycins.

As antibiotics, all macrolides possess antibacterial activity.* Some of the macrolides, including oleandomycin and triacetoxyoleandomycin, erythromycin, leucomycin, spiramycin and acetoxyspiramycin complexes are used clinically and also as supplements in animal feeds.[8] Tylosin is used in preservation of food and also as a supplement in animal feeding.

For the antibiotic activity of the macrolides, both the aglycone (the macrolide with the sugars removed) and sugar moieties are needed. Although the sugars are not active themselves, differences in the sugar moieties linked to the same aglycone cause important differences in the properties and activity of the macrolide. This aspect is elaborated upon later in the section dealing with biological activity. Because of the importance of the sugars, the macrolide antibiotics can be classified according to their sugar components into

---

*The polyene macrolides have little antibacterial activity and are mainly antifungal agents.

Table 1: Macrolide Antibiotics

Name	References	Structurally Defined
Acumycin	9	
Aldgamycin C & E	10	
Amaromycin	11	
Anglolamycin (Shincomycin A)	12	
Azalomycin B	13	
Bandamycin A Bandamycin B (Chalcomycin)	14	1964
Carbomycins (Magnamycins)	3,15	1957, revised 1965
Cirramycin A & B	16	1969
Erythromycins	6,17	1957, revised 1962
Forocidins	18	
Josamycin (Leucomycin A)	19	1970
Kujimycins	20	1969
Lankamycin	21	1964, revised 1970
Leucomycins (Kitasamycins)	19,22	1967
Macrocin	23	
Maridomycin	24	1973
Megacidin	25	
Megalomycins	26	1969
Methymycin	4,27	1956
Miamycin	28	
Narbomycin	29	1962
Neomethymycin	30	1958
Neospiramycins	18	
Neutramycin	31	1969
Niddamycin	32	1962
Oleandomycin (Matromycin)	33	1960
Pikromycin	2,34	1957, revised 1968
Platonomycin	35	
Proactinomycins	36	
Relomycin	37	
Rosamycin	38	
Sekazin	39	
Spiramycins	15f,20a,20d,40	1964, revised 1969
Tertimycins	15d, 41	
Tylosin	42	1970
B-58941	43	1970
SF-837	44	1971
YL-704	45	1971

different groups with common characteristics. For instance, the Methymycin Group contains methymycin, deoxymethymycin, neomethymycin, narbomycin, pikromycin and the forocidins. These macrolides all have an amino sugar linked to the aglycone. The macrolides of the Lankamycin Group (chalcomycin, neutramycin, lankamycin and kujimycin A) on the other hand all contain two non-nitrogenous sugars linked to the aglycone.

The structural elucidation of the macrolide antibiotics has proved to be a difficult chemical problem. The aglycone moiety of many macrolides is unstable under ordinary experimental conditions. Mild basic conditions may cause decomposition of the aglycone through elimination and/or reverse aldol reactions. Under acidic conditions complex alterations of the lactone skeleton may also occur. In order to study the macrolides under simpler conditions, the sugar residues(s) must be removed. In some cases it is possible (e.g. methymycin) to remove the attached sugar (desosamine) while leaving the aglycone intact. However, in the case of erythromycin A, even the mildest conditions needed to remove the desosamine result in extensive degradation of the fourteen-membered lactone ring.[17g] This problem with erythromycin has only recently been overcome by preparing a more stable derivative before hydrolysing the sugars.[46]

The organic chemist is faced with another problem once the free aglycone has been obtained. Because of the numerous multiple branchings on the lactone ring, there are many asymmetric centres. For instance, in erythromycin A, 85% of the aglycone ring carbons are chiral. To obtain fragments of the lactone ring in such a way that there is no chance for epimerization of the asymmetric carbons contained in the fragments is a demanding task. Furthermore, to identify *rigorously* the one correct stereoisomer from the myriad of possible choices in a typical macrolide is so chemically difficult that the chemist has had to resort to X-ray analysis for the full structural elucidation of several macrolides, except in the cases of methymycin and the erythromycins. X-Ray analysis was used to determine or confirm the structures of erythromycin A,[47] erythromycin A carbonate,[48] and a leucomycin derivative,[49,50] demycarosylisoleucomycin A_3. In addition, $\Delta^{4,5}$-anhydropikronolide has also been studied by this technique.[51] The crystal structure of a polyene macrolide, amphotericin B, has also been carried out.[52]

The configurations of other macrolides have been proposed on the basis of chemical and spectroscopic evidence. The methods used include: (1) the correlation of degradation products with substances of known absolute stereochemistry, (2) optical rotary dispersion,

(3) molecular rotation differences and (4) nuclear magnetic resonance (nmr) spectroscopy. This latter technique has been especially useful for two reasons which will be elaborated upon later. Firstly, the aglycones of several macrolides have a single conformation in solution and thus nmr correlations can be drawn. Secondly, the vicinal coupling constants are either small (1-3 Hz) or large (9-11 Hz). As a result, conclusions may often be confidently reached regarding the relative stereochemistry of vicinal substituents.

By using X-ray analysis and correlations obtained using the methods above, reliable total absolute configurations have been assigned for methymycin, oleandomycin, pikromycin, spiramycin and the carbomycins, erythromycins and leucomycins. Important information concerning the aglycones of chalcomycin, lankamycin, narbomycin and neomethymycin is also available.[8]

B) BIOLOGICAL ACTIVITY

As antibiotics, the macrolides possess antibacterial activity.[53] They are active mainly against Gram-positive bacteria and in general have a much reduced activity against Gram-negative organisms, as shown in Table 2.

Table 2: *In vitro* Inhibitory Concentrations of Different Macrolide Antibiotics (μg/ml)

Organism:	Carbomycin	Spiramycin	Methymycin	Lankamycin
Gram-positive bacteria:				
Bacillus subtilis	0.36	3	730	-
Staphylococcus aureus	0.22	1	40	100
Streptococcus pyogenes	0.08	0.6	10.5	100
Streptococcus faecalis	1.3	1	1875	>100
Gram-negative bacteria:				
Escherichia coli	100	31	1875	>100
Aerobacter aerogenes	100	31	1875	-
Klebsiella pneumoniae	3	33	3.2	100
Pseudomonas aeruginosa	60	>1500	1875	>100

The macrolides have very reduced or no activity in eucaryotic cells and thus are of low toxicity and are almost completely lacking in side effects. The mode of action of macrolide antibiotics is primarily bacteriostatic through inhibition of bacterial protein synthesis at the ribosomal level. Little or no inhibition of bacterial ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) synthesis has been observed. However, at concentrations higher than the minimum inhibitory level definite bacteriocidal behaviour is observed.

In order to comprehend the bacteriostatic nature of these antibiotics, it is necessary to have a basic understanding of the mechanism of protein synthesis at the cellular level. This topic is covered in depth in many biology textbooks.[54] However, a brief summary appears to be appropriate and is presented on the following pages.

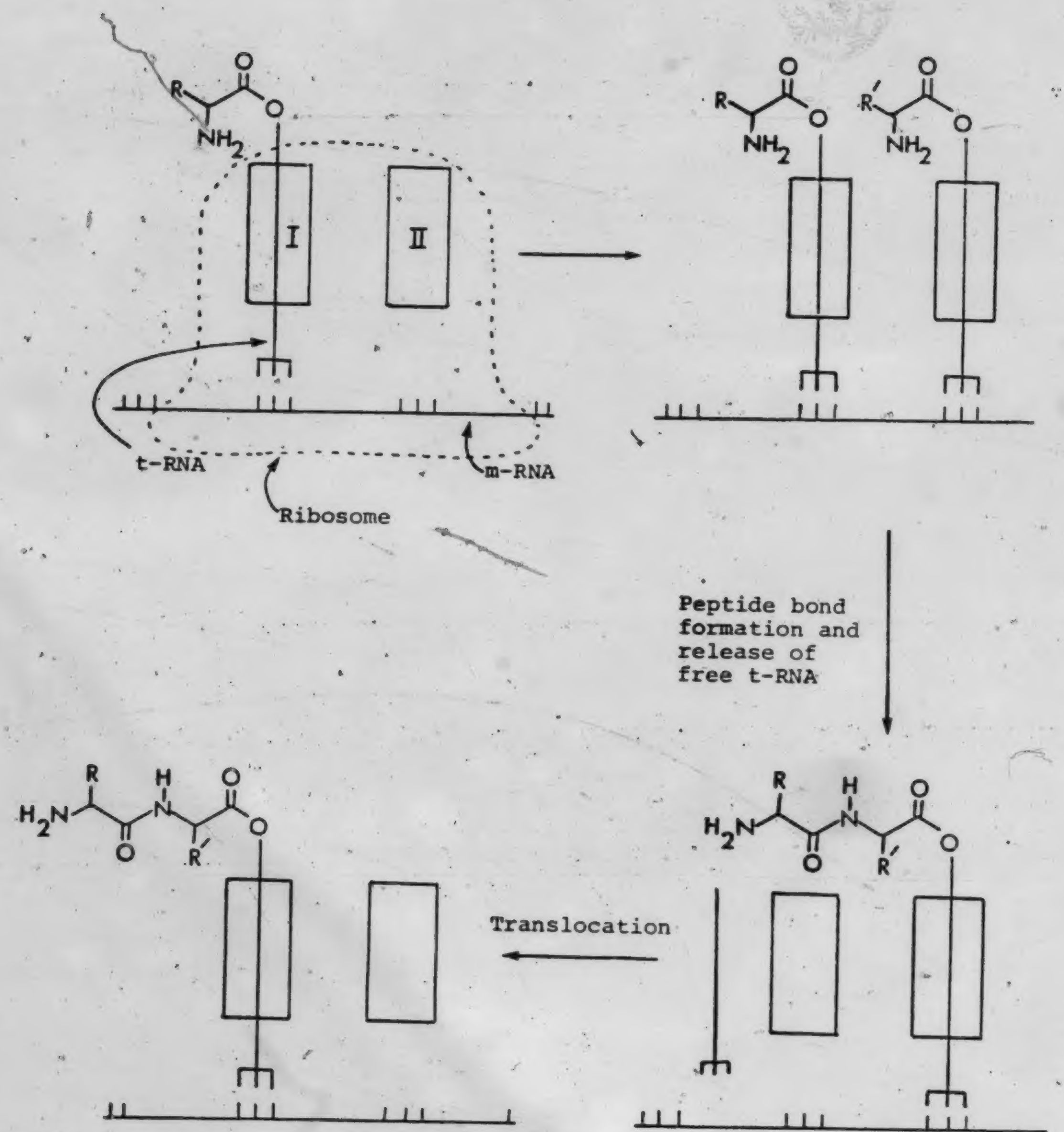
Proteins are formed in the ribosomes of the cell. These ribosomes are bodies in the cytoplasm made up of a special type of RNA and a number of protein chains. In addition, ribosomes consist of a large and a small subunit, the larger of which contains two sites which are very important in the synthesis of protein molecules. The actual formation of a protein molecule involves interaction of a ribosome with transfer RNA (t-RNA) and messenger RNA (m-RNA).

To initiate the protein synthesis, a section of nuclear DNA, the material carrying the genetic code, unravels. A molecule of RNA then forms along one of the two strands of the DNA. The nucleotides of this new molecule are arranged such that they are the base compliments of those in the strand of DNA being copied. This new molecule is the m-RNA and is a template containing the order for the linkage of the amino acids in the protein about to be synthesized. The m-RNA then leaves the nucleus and enters the cytoplasm where it attaches itself to the smaller subunit of the ribosome.

Transfer RNA consists of a loop of RNA which can bind reversably to a specific amino acid with one section of the loop. A group of nucleosides known as the anticodon in another section of the t-RNA is able to hydrogen bond to a fixed section of the m-RNA, known as the codon, much like a key fits a lock. This binding site is determined by the base sequence of the nucleosides of the codon and anticodon, as well as by the geometry of the t-RNA and m-RNA at the junction.

A molecule of t-RNA picks up its amino acid in the cytoplasm and enters Site I of the larger subunit of the ribosome where the linking up of the condon and anticondon occurs. Then a second molecule of t-RNA, possibly bearing a different amino acid, is attached to the m-RNA at Site II of the ribosome. A peptide bond is then enzymatically formed between the two amino acids of the adjacent t-RNA groups, and the t-RNA in Site I is released back into the cytoplasm. This sequence leaves a t-RNA molecule with an attached peptide joined to the m-RNA in the ribosome. This entire complex then moves over into Site I leaving Site II free and ready for the initiation of another cycle of bonding and polymerization. Thus, by this stepwise process a protein is formed. This process is illustrated in Figure 3.

Figure 3: Protein Synthesis


R
NH2
O
I
II
t-RNA
m-RNA
Ribosome
R'
Peptide bond formation and release of free t-RNA
H2N
H
Translocation

All macrolides are believed to inhibit protein synthesis as a consequence of their interaction with the larger ribosome subunit. There is a controversy concerning the reaction(s) which might be affected by the macrolide antibiotics. Most of the experimental evidence suggests that carbomycin and spiramycin type* antibiotics block the peptide bond formation and possibly even prevent initial attachment of the t-RNA to the ribosome.

Antibiotics of the erythromycin group were not found to be inhibitors of initial peptide bond formation in most experiments. However, they appear to inhibit further peptide bond formation once a peptidyl moiety of a certain length has been attained. It has also been suggested that erythromycin might act to stop the complicated step of translocation of the complex from Site I to Site II in the ribosome.

In order to resolve this apparent difference in the modes of action of various macrolides, it has been suggested that there might be a common binding site in the ribosome for the aglycone moiety of the macrolide antibiotic, which is not the centre where peptide formation occurs. The different sugars present in the macrolides then modify the modes of action of the indi-individal antibiotics.

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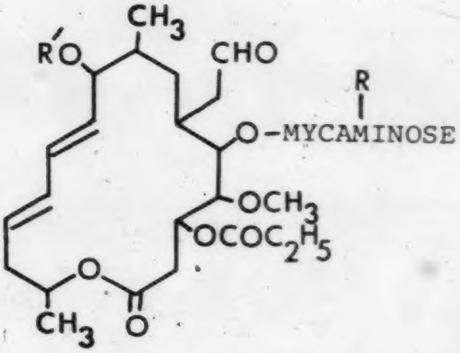
*The grouping of macrolides according to the sugar moiety linked to the aglycone ring was mentioned earlier.

In support of this hypothesis are the results obtained with spiramycin III and its derived antibiotics neospiramycin III and forocidin III which have the same aglycone but lack one and two of its sugars, respectively.



	R	R'
Spiramycin III	Mycarose	Forosamine
Neospiramycin III	H	Forosamine
Forocidin III	H	H

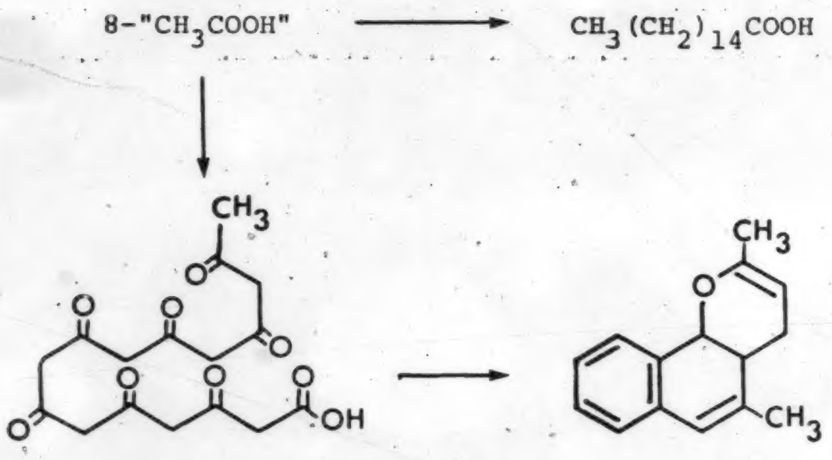
Although having the same aglycone as spiramycin III, neospiramycin III and forocidin III behave in their mode of action similarly to other antibiotics of the Erythromycin and Methymycin Groups, respectively. Incorporation of proline, lysine and phenylalanine into the protein is strongly inhibited by the spiramycin. On the other hand, neospiramycin III and forocidin III are only moderate inhibitors of proline and lysine incorporation and have little or no effect on phenylalanine incorporation. Spiramycin III has also been found to block the donor and acceptor sides of the peptidyl transferase centre in certain systems, whereas the neospiramycin and forocidin have either no inhibitory effect or actually stimulate binding to some extent. It is therefore probable that neospiramycin III and forocidin III bind at the same site in the ribosome as spiramycin III and that it is only the extra sugar residues of the spiramycin which interferes with substrate binding at the peptidyl transferase site.

C) BIOGENESIS OF MACROLIDES

The question of how macrolide antibiotics are synthesized at the microbiological level has received considerable attention. There are three areas of consideration: (1) the series of steps leading to the formation of the lactone ring, (2) the origin of the group of unusual deoxy and amino sugars and (3) the sequence of combination of these portions. These problems will be discussed in order in the following section.

Biogenesis of Macrolide Lactones

In 1907 J. N. Collie suggested that the head-to-tail combination of acetate units to form a poly-β-keto acid (e.g. 1) followed by subsequent cyclization and dehydration could be a biosynthetic pathway for the formation of aromatic natural products.[55] During the 1940's and early 1950's radioisotopic labelling studies



1

2

showed that acetate residues are the primary building blocks of not only aromatic compounds (e.g. eleutherinol 2) but also of fatty acids, such as palmitic acid. By analogy with Collie's hypothesis, K. Gerzon[56] and R. Robinson[57] suggested that similar compounds which appear to contain an extra methyl group might be formed by the incorporation of a propionate unit in the place of an acetate (the Propionate Rule).

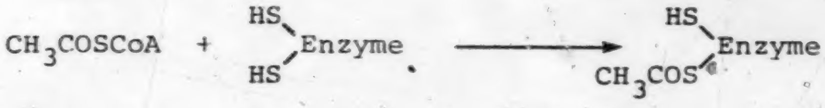
It was not until the latter half of the 1960's that Collie's Polyacetate Rule was modified to give the fatty acid synthetic scheme[58] shown in Figure 4.

The chain lengthening reaction is repeated with condensation of more malonyl-coenzyme A groups until the final release from the enzyme surface at about a sixteen carbon atom compound. Occasionally, a single branched methyl group will be introduced along the sequence to give rise to acids such as 14-methylpalmitic acid. These isolated methyl groups have been shown to arise, not from substitution of a propionate unit for an acetate group, but instead from incorporation of methionine.

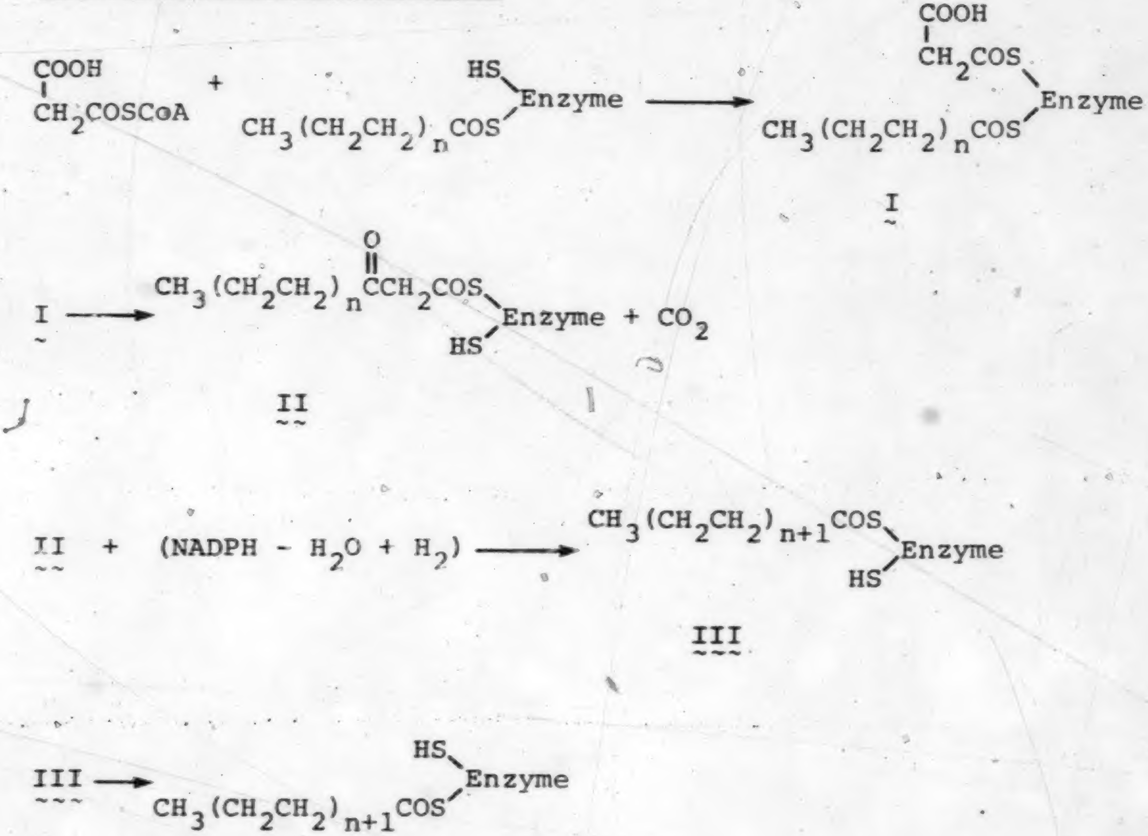
The length of the carbon chain of most macrolide lactones falls in the range of the more abundant fatty acids. For example, palmitic acid contains sixteen carbon atoms, and erythromycin has a fifteen carbon atom chain. However, the lactone rings differ from the

Figure 4: Fatty Acid Biosynthesis

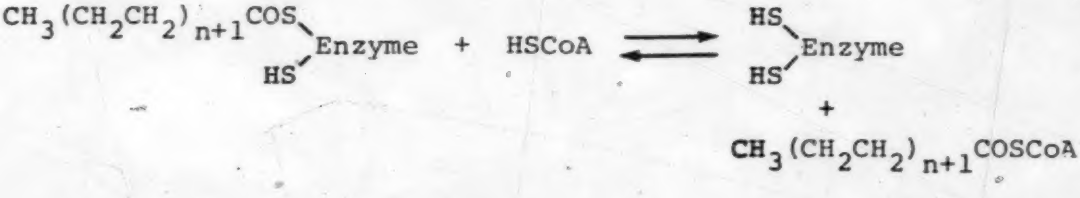
Priming Reaction


CH3COSCoA
+
HS
Enzyme
HS
HS
Enzyme
CH3COS

Chain Lengthening Reactions


COOH
CH2COSCoA
+
HS
Enzyme
CH3(CH2CH2)nCOS
COOH
CH2COS
Enzyme
CH3(CH2CH2)nCOS
I
I
O
CH3(CH2CH2)nCCH2COS
Enzyme + CO2
HS
II
II + (NADPH - H2O + H2)
CH3(CH2CH2)n+1COS
Enzyme
HS
III
III
HS
Enzyme
CH3(CH2CH2)n+1COS

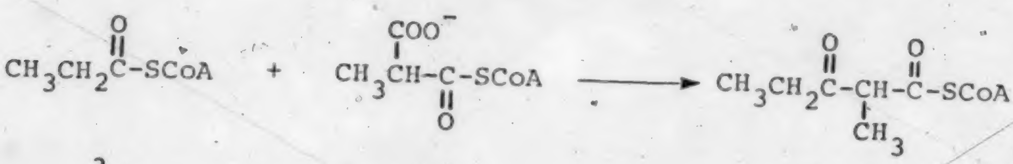
Termination Reaction


CH3(CH2CH2)n+1COS
Enzyme
HS
+ HSCoA
HS
Enzyme
HS
+
CH3(CH2CH2)n+1COSCoA

common fatty acids in two respects; they contain multiple branching and they are highly oxygenated along the chain.[59]

One hypothesis for the biosynthesis of macrolides was based on the similarity in chain length with fatty acids and their ability to occasionally incorporate methyl groups along the chain as in 14-methylpalmitic acid. Birch _et al_.[60] suggested that the basic carbon skeleton of the lactone is derived from acetate units. The methyl groups, originating with methionine, choline, or an equivalent one-carbon donor, are then inserted at the active methylene positions along the chain. This theory was postulated before the fatty acid biosynthesis was modified as outlined above, and was compatible with the belief of the time that the fatty acids were derived by dehydration of a poly-β-keto acid chain.

With the elucidation of the carbon skeleton of erythromycin (see Figure 1) by Wiley and coworkers,[17a,c,g] Gerzon[61] and Woodward[3] recognized that erythromycin follows perfectly the three-carbon regularity defined by the Propionate Rule. The theory was then advanced[62] by analogy with the fatty acid biosynthesis, that the macrolides can be formed from propionyl-coenzyme A 3 and methyl malonyl-coenzyme A 4 as illustrated in the following equation.



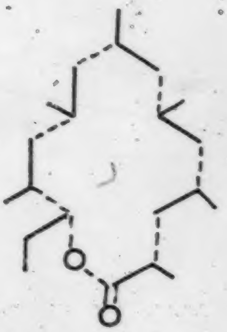
$$CH_3CH_2\overset{\overset{O}{\|}}{C}\text{-SCoA} \quad + \quad CH_3\overset{\overset{COO^-}{|}}{CH}\text{-}\underset{\underset{O}{\|}}{C}\text{-SCoA} \longrightarrow CH_3CH_2\overset{\overset{O}{\|}}{C}\text{-}\underset{\underset{CH_3}{|}}{CH}\text{-}\overset{\overset{O}{\|}}{C}\text{-SCoA}$$

3 4 5

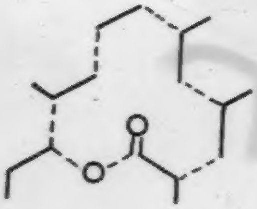
Unit 5 then condenses further with additional methyl malonyl-coenzyme A without loss of the carbonyl groups as occurs in the fatty acid synthesis outlined above. This pathway is then somewhat analogous to the mechanism proposed originally by Collie. When the chain has reached the appropriate length, lactone ring formation occurs by intramolecular esterification with concomitant removal of the macrolide from the enzyme surface.

So far as the final products are concerned, the alternatives of Birch, and of Gerzon and Woodward are structurally equivalent. The validity of the propionate hypothesis was demonstrated by tracer studies of the methymycin biosynthesis from Streptomyces venuzuelae.[63] Fermentation in the presence of (methyl-^{14}C) methionine gave methymycin labelled almost exclusively in the desosamine residue. Sodium (carboxy-^{14}C) propionate was utilized as a unit with negligible redistribution of the isotopic carbon, and assay results carried out on the degradation products indicated that the methymycin aglycone is built up from five propionate units and one acetate unit. These two results refute the theory postulated by Birch.

The propionate pathway was further confirmed by labelling studies done on erythromycin.[64] It was observed that (carboxy-^{14}C) propionate was incorporated into erythronolide[65] but not into the attached sugars, desosamine and cladinose. The reverse was true when the precursor was (methyl-^{14}C) methionine.[65] In addition, propionate was incorporated into erythromycin to a much greater extent than was acetate.[65c,d] As in methymycin there was little scrambling of the propionate labels. Degradation studies similar to those done on methymycin indicated that erythronolide is derived from seven propionate units.[65a,c]



erythromycins



methymycin
neomethymycin

The above discussion is valid for the smaller macrolide antibiotics, i.e. those with twelve- and fourteen-membered aglycones. Recent studies using carbon-13 magnetic resonance (cmr) techniques have established that there are slightly modified biosynthetic pathways for the production of larger macrolides. For instance, Leucomycin A_3[66] and tylosin,[67] both with sixteen-membered aglycones, have been found to incorporate butyrate, propionate and acetate.

Biogenesis of Macrolide Sugars (See Figure 2)

D-Glucose, a standard nutrient of culture media, has been shown to be the primary building block of the macrolide sugars.[68] For example, when Streptomyces erythreus was incubated with D-glucose-1-^{14}C, -2-^{14}C, or -6-^{14}C, the bulk of the label was found at the corresponding carbon of desosamine. Based on these labelling studies with glucose, the series of oxidations, reductions and alkylations necessary to produce the final macrolide sugars must occur without cleavage of the carbon chain of glucose. In addition, methionine, although not involved in the biosynthesis of methynolide or erythronolide, is incorporated efficiently into the sugars desosamine and cladinose as mentioned above. Degradation of the sugars obtained using (methyl-^{14}C) methionine as the precursor established that in desosamine all radioactivity was located in the dimethylamino function, whereas in cladinose the label was equally distributed between the O-methyl and the C-methyl at C_3.

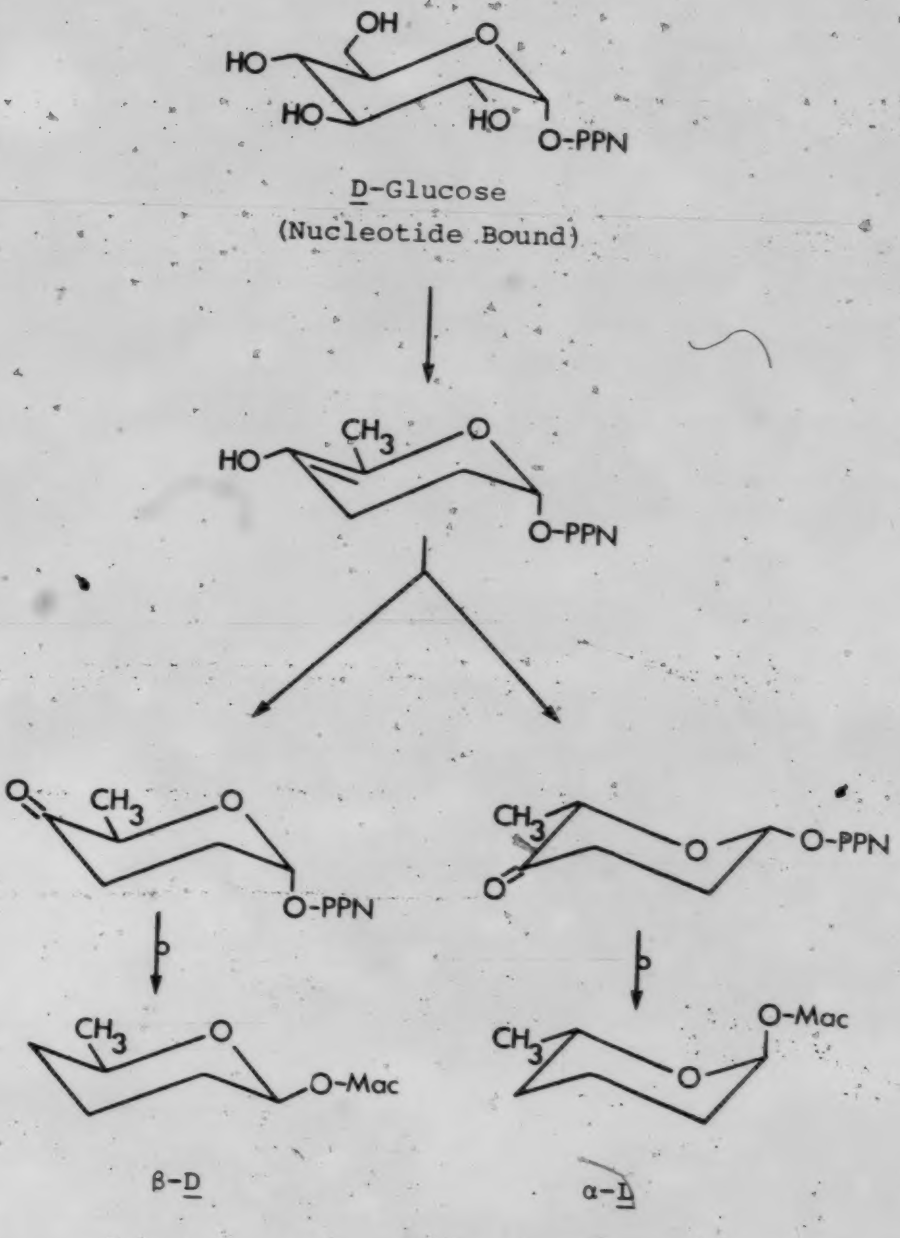
In order that the necessary conversions can be carried out without opening of the glucose ring, and to account for the fact that all macrolides have the same absolute configuration at their anomeric centres, Celmer[69,70] proposed that D-glucose is bound to a nucleotide during its conversion to the macrolide 6-deoxy sugars as illustrated in Figure 5. This idea of D-glucose being bound to a nucleotide during its reactions is precedented.[71] For instance, the isolation of thymidine diphosphate-4-keto-6-deoxy-D-glucose during the conversion of D-glucose into L-rhamnose has been reported.[68c] The nucleotide is retained in the intermediates until the final transfer of the deoxy sugar to the macrolide lactone.

Sequence of Combination

It has been shown that the intact lactone ring of erythromycin B (Figure 1), erythronolide B, could be isolated from Streptomyces erythreus.[72] When this was done, after growing the organism in the presence of ^{14}C-labelled propionate, the erythronolide had a high specific incorporation. This labeled lactone was reintroduced into a fresh culture and the isolated erythromycins were shown to be radioactive. These results strongly suggest that the erythromycin sugars are attached to the fully formed lactone rather than at an earlier stage in the biosynthesis.

Similarly, studies reported by M. Suzuki[73, 74] have further substantiated this combination sequence.

Figure 5: Biosynthesis of Macrolide Sugars


OH
HO
HO
HO
O
O-PPN
D-Glucose
(Nucleotide Bound)
CH_3
HO
O
O-PPN
O
CH_3
O
O-PPN
CH_3
O
O-PPN
O
CH_3
O
O-Mac
CH_3
O
O-Mac
β-D
α-D

Evidence was presented for the initial synthesis of the aglycones followed by the later attachment of desosamine in the biosynthesis of pikromycin and narbomycin.*

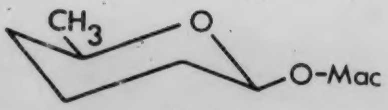
---

*Private communication of February 28 1976 from Professor D. Perlman, University of Wisconsin: Our synthetic methynolide, when added to the oleandomycin-producing streptomycete, has been converted into antimicrobially active material, very likely methymycin.

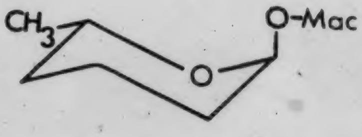
D) A CONFIGURATIONAL MODEL FOR MACROLIDES

It had become apparent by the early 1960's that among the macrolides whose constitution had been defined there were extremely interesting similarities. The lactone rings of the erythromycins[17a,c,g,h] oleandomycin,[33a] narbomycin,[29a] methymycin[4] and its isomer neomethymycin[30a,b] all followed the poly-β-keto acid biogenetic scheme, and are made up predominantly or exclusively from propionate units. In addition, the amino sugar D-desosamine is found in each of these antibiotics. This sugar is known to be attached in the β-configuration to erythromycins A[69,75] and B,[69,76] and to oleandomycin.[69,76,77] The aglycones of these three macrolides were also linked to then unknown 2,6-deoxy sugars through α-L glycosidic bonds.[69,76,77]

8

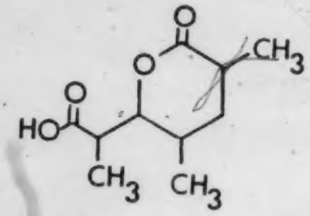


β-D



α-L

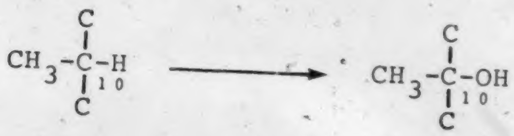
In other words, the glycosidic linkages of several constitutionally defined macrolides have identical chirality. Further evidence of the close stereochemical relationships between various macrolides is the isolation of the Djerassi-Prelog lactonic acid (+)-6 from the degradation of methymycin, neomethymycin, pikromycin, and narbomycin.



(+)-6

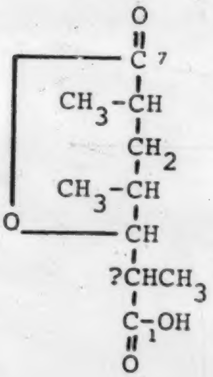
On the basis of these similarities, W. D. Celmer suggested in 1964 that there is a common pattern of stereochemistry that would be obeyed by all macrolides.[76] Over the next two years Celmer refined his original model to give a tool which has successfully predicted the stereochemistry of all macrolides tested.

In many macrolides there are oxygen functions at sites that do not correspond to carbonyl locations in the poly-β-keto acid precursor.[3] These "extra" oxygens are believed to be introduced by oxidation at a late stage in the lactone biosynthesis. Experiments involving the biosynthesis of pikromycin and its 12-deoxy isomer narbomycin have confirmed this hypothesis.[73,74] On the basis of previous evidence that bio-oxidations take place with retention of configuration, Celmer proposed that the orientation of a methyl group at a chiral, lactonic carbon should remain uneffected when a hydroxy group (an "extra" oxygen) is introduced at that centre late in the macrolide biosynthesis. M. Suzuki[78] showed that 10-deoxymethymycin can be biologically converted into methymycin, thus bearing out this hypothesis in the case of the C_{10} centre of methymycin which is shown below in Fischer projection.

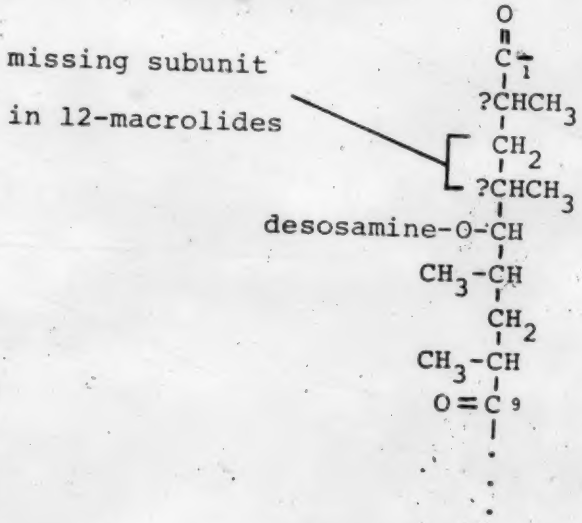


$$\mathrm{CH_3-\overset{\displaystyle C}{\underset{\displaystyle C}{C}}{}_{10}-H} \longrightarrow \mathrm{CH_3-\overset{\displaystyle C}{\underset{\displaystyle C}{C}}{}_{10}-OH}$$

As mentioned above, Celmer had several facts at hand when he started his work. The four asymmetric centres of the Djerassi-Prelog lactonic acid (+)-**6** were known to correspond to C_2, C_3, C_4 and C_6 of methymycin and neomethymycin, and to C_4, C_5, C_6 and C_8 of narbomycin. In addition, the C_4 and C_6 centres of the lactonic acid unquestionably had the *S* and *R* configuration, respectively.[30c,d] In order to correlate the chiral centres of the twelve- and fourteen-membered lactones, Celmer proposed that the penultimate propionate unit had been skipped during the biosynthesis of the twelve-membered ring.[69,76] Applying Hudson's Rule to (+)-6 (shown below in Fischer projection), Celmer tentatively assigned it as a D-lactone, and thus C_3 would have the S configuration.[69]


O
C 7
CH_3-CH
CH_2
CH_3-CH
O
CH
?$CHCH_3$
C-OH 1
O

(+)-6


missing subunit
in 12-macrolides
O
C 1
?$CHCH_3$
CH_2
?$CHCH_3$
desosamine-O-CH
CH_3-CH
CH_2
CH_3-CH
O=C 9

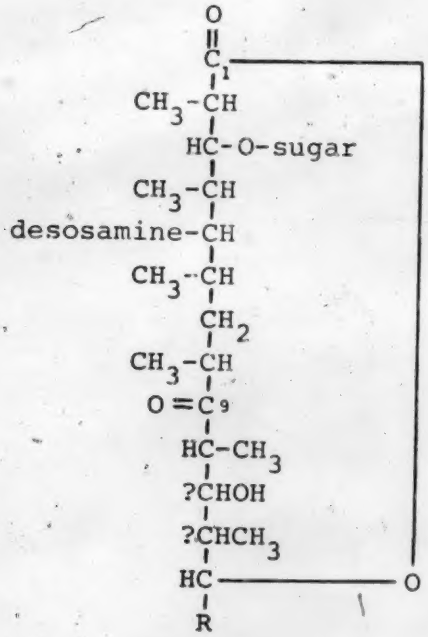
7

With this data, a preliminary model for macrolide stereochemistry 7 could then be drawn. Fischer projection is also used in this diagram.

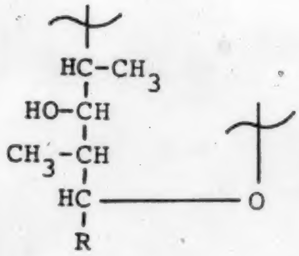
Gerzon et al.[61] proposed a configurational model of 9-dihydroerythromycin A in 1956. Combining Gerzon's assignments with those used in 7, Celmer elaborated his model by assigning stereochemistry at C_2, C_3, C_4,

C_{10} and C_{13} to give 8. Only the chirality at C_{11} and C_{12} remained to be defined, although many of the assignments in 8 required further support.

Degradation studies with anhydro-oleandomycin allowed the orientations of the last two centres to be specified, as well as confirming several previous assignments. Celmer was now able to complete his model 9.


O
C1
CH3-CH
HC-O-sugar
CH3-CH
desosamine-CH
CH3-CH
CH2
CH3-CH
O=C9
HC-CH3
?CHOH
?CHCH3
HC
O
R

8


HC-CH3
HO-CH
CH3-CH
HC
O
R

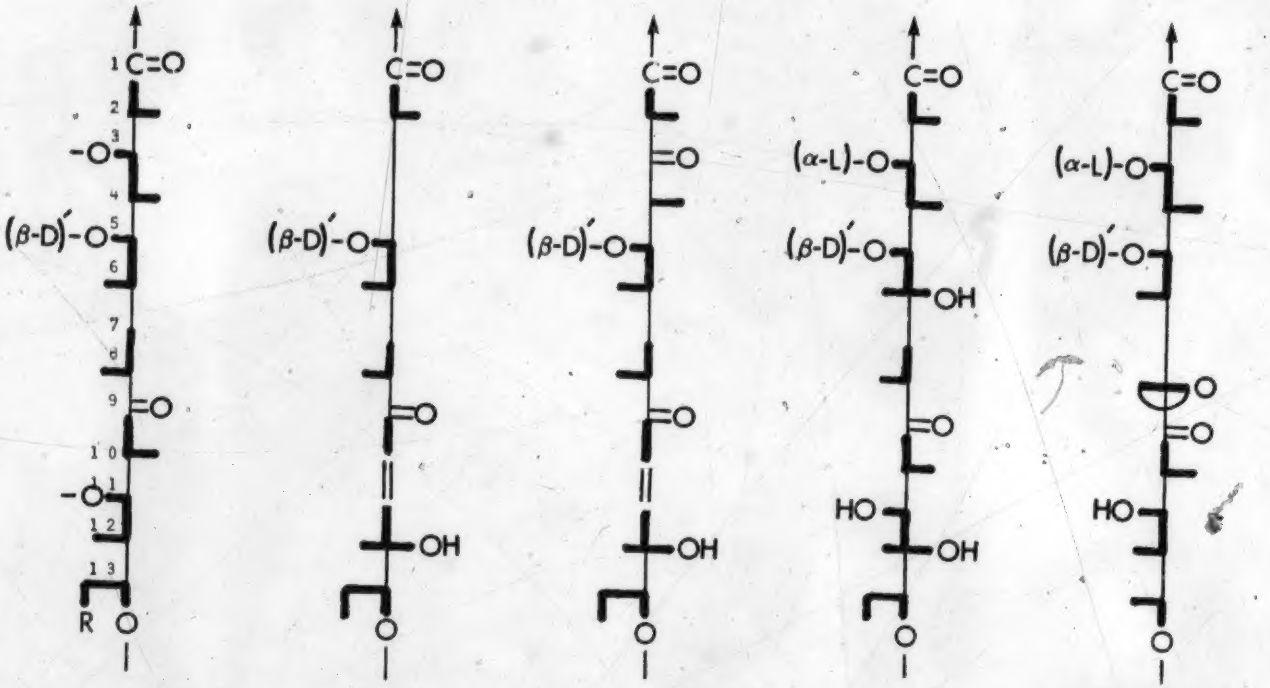
9

Further experiments showed that Gerzon's erythromycin assignments may have been incorrect.[79] A reinvestigation of the problem led Celmer to conclude that the configurations at C_2, C_3 and C_4 must be reversed.[80-82] The final model is presented in schematic form in Figure 6 along with several macrolides to illustrate the congruence of the skeletal stereochemistry.

Celmer's model correctly predicts the stereochemistry in the twelve-membered macrolides by assuming that the penultimate propionate unit is skipped during the biosynthesis, as is mentioned above. The sixteen-membered lactones can be correlated with the model by postulating that an extra acetate unit has been inserted between the third and fourth subunits of the model. Furthermore, the stereochemistry of the hydroxy groups that originate from bio-reduction of the carbonyls of the acetate subunits is also predictable. Slight modifications of the model have allowed correct assignments to be made in cases of unusual macrolides. The model has to date withstood all tests. Reexamination of the experiments used as a basis for contradicting the model have in each case shown the original conclusions to be in error!

In conclusion, the model depicts: (1) the chirality at lactone centres bearing oxygen functions that are derived from bio-reduction of the carbonyl groups in the poly-β-ketone, (2) the chirality of alkyl substituents at lactone centres, (3) all carbohydrate components as 6-deoxypyranosides with identical chirality (either β-D or α-L) at the anomeric carbons and (4) C_5 (or its equivalent) carrying a β-D-glycoside.

Figure 6: Celmer's Model for Macrolide Stereochemistry


1
2
3
4
5
6
7
8
9
10
11
12
13
C=O
-O
(β-D)′-O
=O
R
O
OH
(α-L)-O
HO

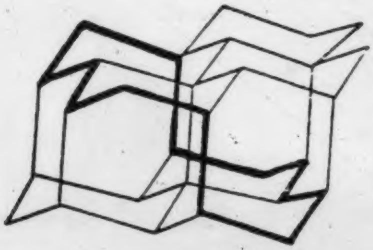
MODEL METHYMYCIN PIKROMYCIN ERYTHROMYCIN A OLEANDOMYCIN

The model makes no predictions about either the chirality at exocyclic centres or the chirality of an extra oxygen attached at a ring carbon originally a methylene group of an acetate subunit in the poly-β-ketone. A more detailed description of the steps used in defining the model, and the challenges it met can be found in a review article by W. D. Celmer.[70]

E) CONFORMATIONAL ANALYSIS OF MACROLIDE AGLYCONES

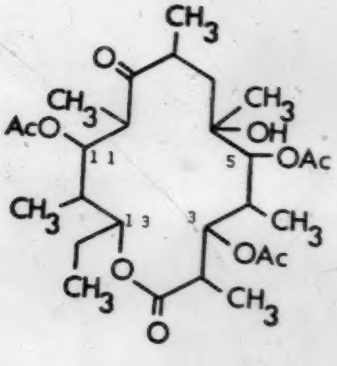
The fourteen-membered macrolides were the first compounds of this class to be studied by conformational analysis primarily because of their availability as a consequence of their chemotherapeutic importance.

In 1963, Dale[83] proposed a conformational model of cyclotetradecane on the basis of theoretical energy considerations. He suggested that if a particular ring can be superimposed on the diamond lattice such that all ring carbons lie on lattice points, then the resulting conformation of the ring is free of Baeyer strain. The ring of cyclotetradecane could be placed on the diamond lattice as shown below.



Molecular optical rotation studies[70] of oleandomycin, a fourteen-membered macrolide, and its derivatives showed that the removal of the large sugar residues did not drastically alter the aglycone conformation. This observation led Celmer[69,82] to suggest that the oleandomycin aglycone might be fixed and possibly could be fitted onto the diamond lattice with the same conformation as cyclotetradecane. He also suggested that erythromycin might follow similar geometric lines.

Perun et al.[84] built upon this idea and experimentally determined that a single conformation of erythonolide was present in solution by making use of proton magnetic resonance (pmr) and circular dichroism (CD) techniques. Because of the relative insolubility of erythonolide B in most non-polar solvents, the most detailed studies were carried out using 3,5,11-triacetoxyerythronolide B 10.



10

The methine protons at C_3, C_5, C_{11} and C_{13} of **10** were of major significance in this study since the signals due to these protons were well separated from other resonances due to oxygenated substituents and showed distinctive splitting patterns. Variable temperature experiments from -80° to 110° showed little effect on the coupling of these protons. There was also little variance in the J values in solvents of very different polarities. Since it had been established that there is a solvent dependence for the populations of conformational isomers which are in equilibrium, as reflected by changes in the average coupling constants for the molecule,[85] then the absence of solvent effect in the erythronolide indicated the presence of a single conformational isomer.

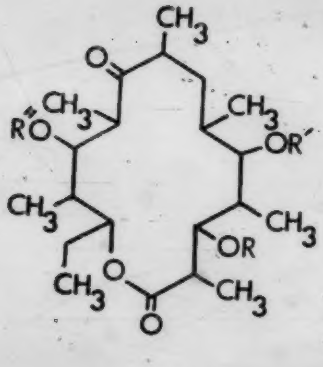
The magnitudes of the vicinal coupling constants in the erythronolide were either large (10-12 Hz) or small (0-2 Hz). If the aglycone were flexing, then the observed coupling constants would have intermediate values, assuming that the various conformers were all significantly populated.[85,86] The observation of only these two distinguishable sets of coupling constants further indicated that a single conformational isomer was present.

Conformational rigidity was also indicated by CD studies at various temperatures and in different solvents.[84]

All of these facts pointed to the presence of a single conformational isomer.

Perun found that the most useful model compounds for a conformational assignment were 6-deoxyerythronolide B 11a and its acetate derivatives 11b-f since these compounds have vicinal proton substituents at every ring position except those occupied by the ketone and lactone groups and thus provided the most useful experimental data.

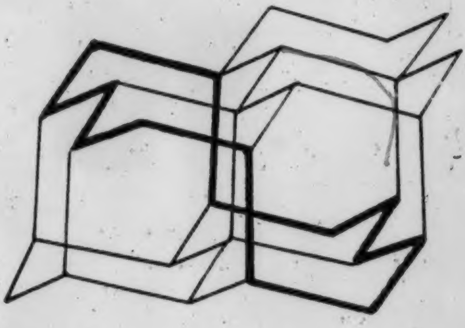
By using the Karplus relationship,[87] the dihedral angles at each position could be determined with reasonable assurance. In this way a model of 11 could be placed in the Celmer-Dale conformation as shown in Figure 7a.



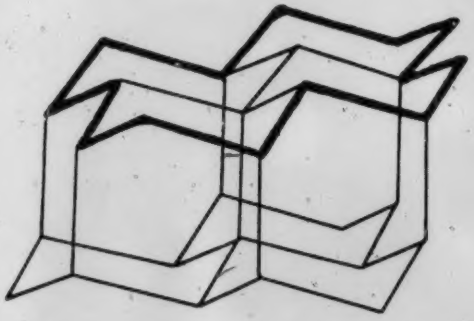
11

	R	R'	R"
a	H	H	H
b	acetyl	H	H
c	H	acetyl	H
d	H	H	acetyl
e	acetyl	acetyl	H
f	acetyl	acetyl	acetyl

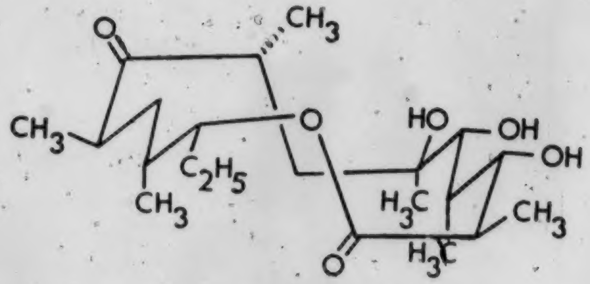
Figure 7: Conformation of Erythronolide B



Dale C-14 Diamond Lattice

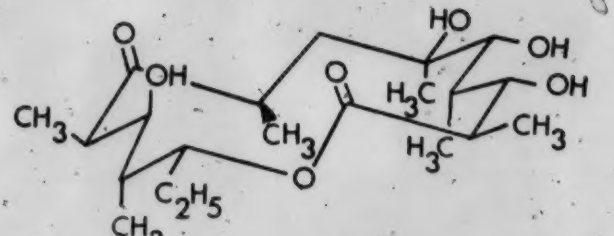


Alternate C-14 Diamond Lattice


O
CH$_3$
CH$_3$
O
HO
OH
OH
C$_2$H$_5$
CH$_3$
H$_3$C
CH$_3$
O
H$_3$C

Celmer Conformation

7a


HO
O
OH
O
OH
OH
CH$_3$
H$_3$C
CH$_3$
CH$_3$
H$_3$C
O
C$_2$H$_5$
CH$_3$

Perun Conformation

7b

Although the agreement of the pmr parameters with the conformation proposed by Celmer was good, further consideration revealed several discrepancies that indicated that this conformation was neither a favoured low-energy conformation nor consistent with other physical data. Molecular models of the Celmer Conformation showed that an unfavourable 1,3-syn-periplanar interaction between the C_4- and C_6-methyl groups was present as well as a severe interaction between the C_{12}-methyl and the lactone carbonyl group. Moreover, it was believed that aglycones of a single family were apparently similar in conformation, and yet Celmer's model did not agree with the known conformation of erythromycin A which had been established by X-ray analysis.

A re-examination of the criteria used in the selection of the most favourable diamond lattice conformation disclosed an alternate lattice which had not been considered before. A slight modification of this conformation, as suggested by Perun, incorporated the relative positions of the ring protons and other substituents in a manner which satisfies both the pmr and X-ray data for erythronolide. The alternate diamond lattice and the Perun Conformation are shown in Figure 7b. Further evidence for Perun's model was provided by CD studies. When the well known Octant

Rule as modified for moderately twisted systems was applied to the ketone chromophore of erythronolide in the Perun Conformation, a negative peak was predicted for the ketone absorption in the CD curve. This was observed. Predictions based on Celmer's model were inconsistent with this finding. Similarly for the lactone chromophore; Celmer's model gave a wrong prediction while use of Perun's model led to the correct prediction of the observed spectrum.

The Perun Conformation, therefore, appeared to satisfy all of the physical data available for the aglycone at the time.

More recent detailed analyses of the pmr and CD spectra of derivatives of erythronolide B have suggested that there is some limited conformational freedom in this aglycone.[88a] The general diamond lattice conformation proposed by Perun is maintained with subtle modification in either the C_2 through C_5, or C_6 through C_9 segments depending on the nature and position of ring substituents. Variable temperature measurements in a series of acetoxy derivatives have indicated that the conformational changes in these two regions are interdependent. This fact enabled the determination of the limiting conformations which are populated to different extents in the series. Conformational analyses of pikromycin, narbomycin, and their derivatives using pmr and CD techniques have also been carried out.[88b]

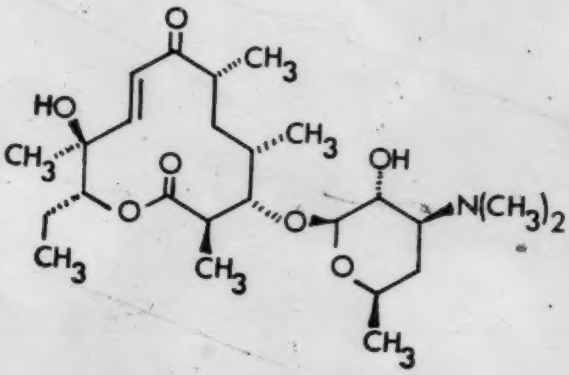
Investigation of the conformation of macrolides has now been extended with the use of cmr techniques. The signals for carbons in various fourteen-[89] and sixteen-membered[90] macrolides have been assigned. This technique has been useful in ascertaining hydrogen bonding and in the structural analysis of several macrolides. As an example, cmr has allowed the hitherto unknown anomeric configuration of the forosamine moiety of the spiramycins, as well as the location of the disaccharide unit in tylosin, to be determined.[90] Cmr has also been used to determine slight conformational differences between similar aglycones, e.g. erthyronolides A and B.

In conclusion, macrolide lactone rings of the same size all have approximately the same, fairly rigid conformation. The precise shape of the aglycone is however influenced by the various substituents on the ring. These changes in conformation may be investigated using the powerful techniques of pmr and cmr spectroscopy.

CHAPTER 2

PROPERTIES AND CONSTITUTION OF METHYMYCIN

Methymycin was the first of the macrolide antibiotics to have its constitutional structure determined (1956). This work was carried out by C. Djerassi and coworkers[4] at Wayne State University. However, it took an additional fourteen years before the stereochemistry of methymycin 12 was determined by Rickards *et al.*[91]



12

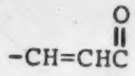
Perhaps an important reason for the slow progress in the elucidation of the stereochemistry of this antibiotic was that interest in methymycin waned when it became apparent that it had no chemotherapeutic value when compared, for instance, to erythromycin. Although methymycin exhibits roughly the same range of biological activity as many other macrolides, its inhibitory power is much less (10^2 to 10^3 fold) as can be seen by studying the table in Chapter 1 Section B dealing with the biological activity of the macrolides.

By 1953 a group of investigators at the Squibb Institute for Medical Research reported the isolation of a new crystalline* (mp 195.5-197°) metabolite, methymycin, from Streptomyces venezuelae.[27] This substance exhibited activity against certain Gram-positive bacteria. The same chemists characterized methymycin as a dextrorotatory base (+62°, methanol; +74°, chloroform) with an empirical formula $C_{25}H_{43}NO_7$. The ultraviolet (uv) spectrum indicated the presence of an α,β-unsaturated carbonyl chromophore. This conclusion was supported by infrared (ir) absorptions in chloroform solution at 1681 and 1628 cm^{-1} and by polarographic studies. The ir spectrum also contained a strong hydroxy band at 3414 cm^{-1} as well as a second carbonyl stretching band at 1719 cm^{-1} that was later ascribed by Djerassi et al. to an ester or lactone. Standard degradative procedures showed the presence of at least six C-methyl groups and a tertiary dimethylamine. The known information is summarized below:

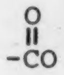
---

*Suitable crystals for an X-ray determination of the structure of methymycin have not been obtained from either the natural or synthetic (this thesis) macrolide.

Methymycin ($C_{25}H_{43}NO_7$) —



$-CH{=}CH\overset{O}{\overset{\|}{C}}$



$-\overset{O}{\overset{\|}{C}}O$

at least 6 $C-CH_3$

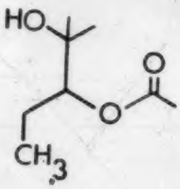
$C-N(CH_3)_2$

at least one OH

5 unsaturated sites; 3 of which are accounted for

Djerassi and coworkers extended the work of the Squibb group and successfully pieced together the total structure of methymycin during the next three years.[4,92] This structural work must be deemed as one of the remarkable achievements of the time, since techniques indispensible to today's research such as pmr, cmr and mass spectral fragment analyses were unavailable to organic chemists of the mid-1950's. Mild catalytic hydrogenation of methymycin reduced only the carbon-carbon double bond of the α,β-unsaturated carbonyl. However, under more severe conditions the enone system was reduced to the corresponding saturated alcohol, tetrahydromethymycin. In addition, a hydrogenolysis product, tetrahydrodesoxymethymycin, in which some oxygen other than the one of the unsaturated carbonyl had been lost, was isolated. Reaction of tetrahydromethymycin with 3-chloroperbenzoic acid yielded only the corresponding N-oxide. All of the unsaturation sites in methymycin had now been accounted for; methymycin contains two rings.

Methymycin was found to contain two hydroxy groups which could be acetylated but which were very resistant to oxidation. Although methymycin itself was inert to periodic acid, reduction with lithium aluminum hydride followed by periodic acid treatment produced good yields of propanal. Thus, methymycin must contain a masked glycol in which one of the hydroxy groups is protected as an ester or lactone. On this evidence, structural fragment 13 was considered to be a part of methymycin. The remaining hydroxy group was also assumed to be tertiary in order to account for its oxidative resistance.

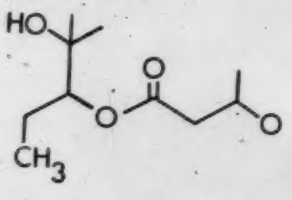


13

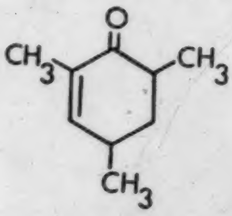
By this stage of the investigation it was evident that the chemical properties of methymycin strongly resembled those of erythromycin and pikromycin, antibiotics known to contain a lactone linked to the basic sugar desosamine.[5,6] Fortunately, in the case of the antibiotic methymycin, its attached sugars could be chemically removed without destroying the aglycone. Hydrolysis of methymycin in aqueous sulphuric acid under carefully selected conditions provided the desosamine salt and a 20% yield of the free aglycone, methynolide 14 ($C_{17}H_{28}O_5$). The structure and stereochemistry of the desosaminyl residue were determined by the standard methods of carbohydrate chemistry and will not be discussed in this thesis.

$$\underset{12}{\text{methymycin}} \longrightarrow \underset{14}{\text{methynolide}} + \text{desosamine}$$

The hydroxy group freed by removal of the desosamine was oxidized to the corresponding ketone. Treatment of this oxidation product with aqueous base followed by acidification liberated 0.6 equivalents of carbon dioxide. Thus the desosaminyl residue was located on the carbon β to the lactone carbonyl. This information allowed the partial structure of methymycin to be extended to 15. The information required to complete the structure was provided by two more experiments.

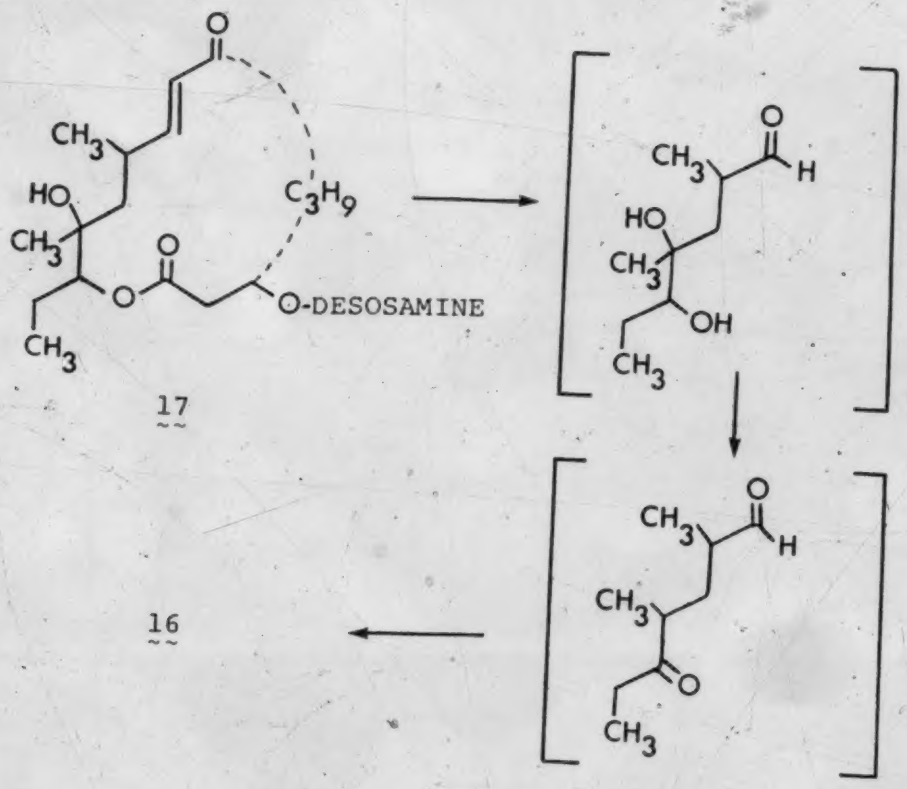


15



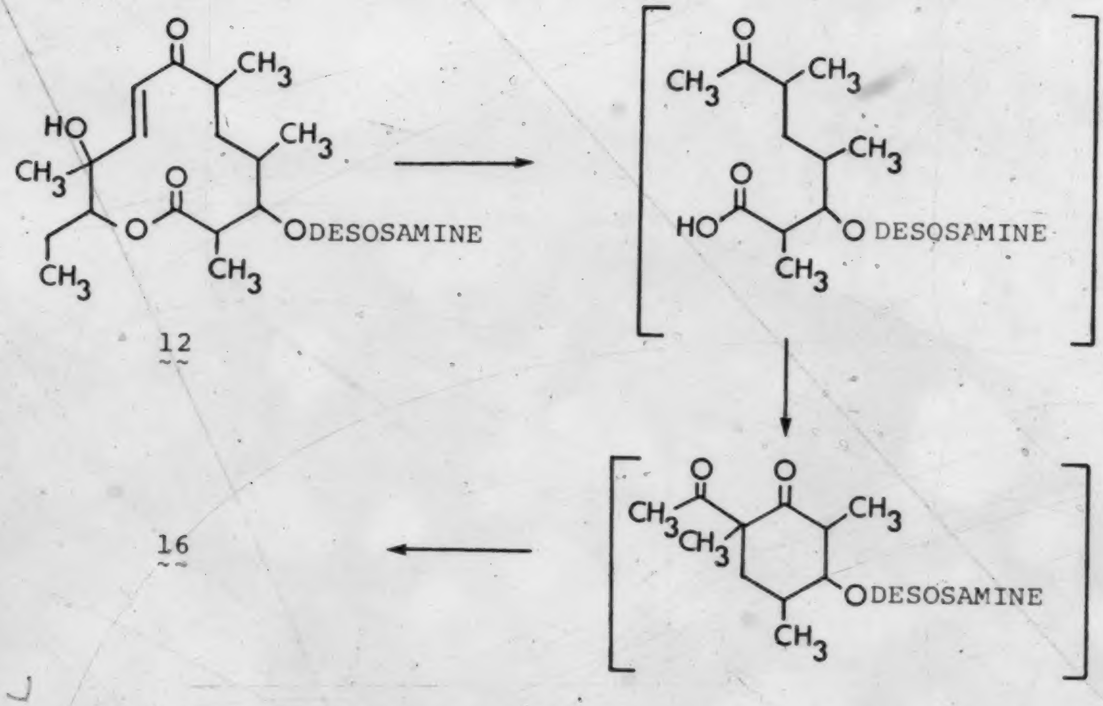
16

Degradation of methymycin by alkali fusion (potassium hydroxide, 360°) produced 2,4,6-trimethyl-2-cyclohexenone **16**. Assuming that **16** was likely formed from an aldol condensation of an aglycone fragment, then two possible ways (**17** and **12**) were suggested to complete partial structure **15**.


O
CH3
HO
CH3
C3H9
O
O
O-DESOSAMINE
CH3
O
CH3
H
HO
CH3
OH
CH3
O
CH3
H
CH3
O
CH3

17

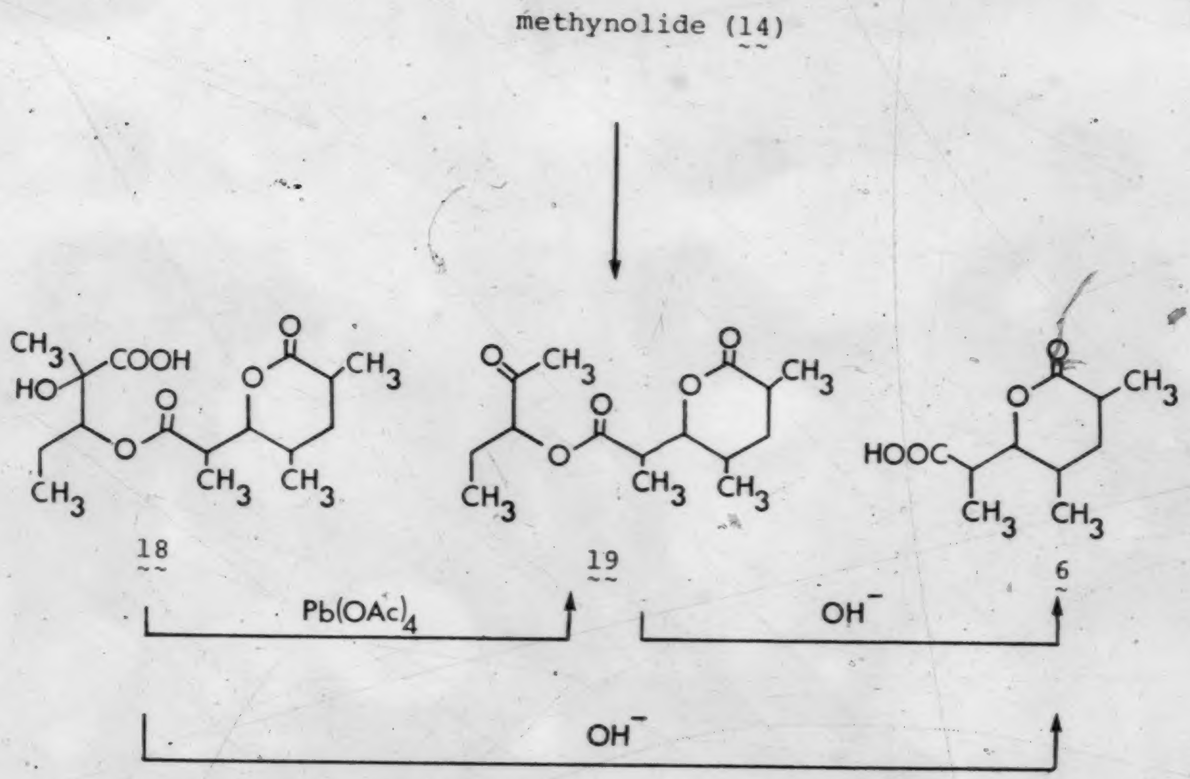
16



12

16

Mild permanganate oxidation of methynolide provided the final evidence that 12 was indeed the structure of methymycin. Three crystalline substances 18, 19 and 6 were isolated from this oxidation. The smallest fragment 6 was identical to the lactonic acid isolated earlier from pikromycin and narbomycin by V. Prelog *et al.*,[93] and identified by them as the δ-lactone of 3-hydroxy-2,4,6-trimethylheptanedioic acid. These findings were completely in accord with structure 12. In addition, the interconversions and properties of these oxidation products were so demanding that methymycin had to have structure 12.

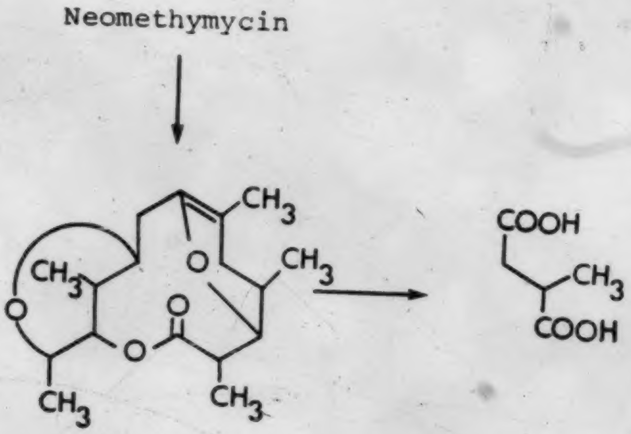


Stereochemistry of Methymycin

Pyrolysis of the Djerassi-Prelog lactonic acid **6** with subsequent ozonolysis produced meso-α,α'-dimethylglutaric acid.[93] This degradation established that the stereochemistry of the C_4- and C_6- methyl groups of **6** must be cis.

In 1957 Djerassi et al.[30b] reported the structure of neomethymycin (see Figure 1), an isomer of methymycin. Since oxidative cleavage of the neomethymycin aglycone also gave **6**, then the stereochemistry of centres C_2 through C_6 must be the same in the two isomers. Acid hydrolysis converted neomethymycin into **20** in high yields.[30a,c]

Degradation of 20 allowed C_4 to be isolated as (-)-S-methylsuccinic acid 21. Consequently C_4 of methymycin has the S configuration and therefore C_6 the R.

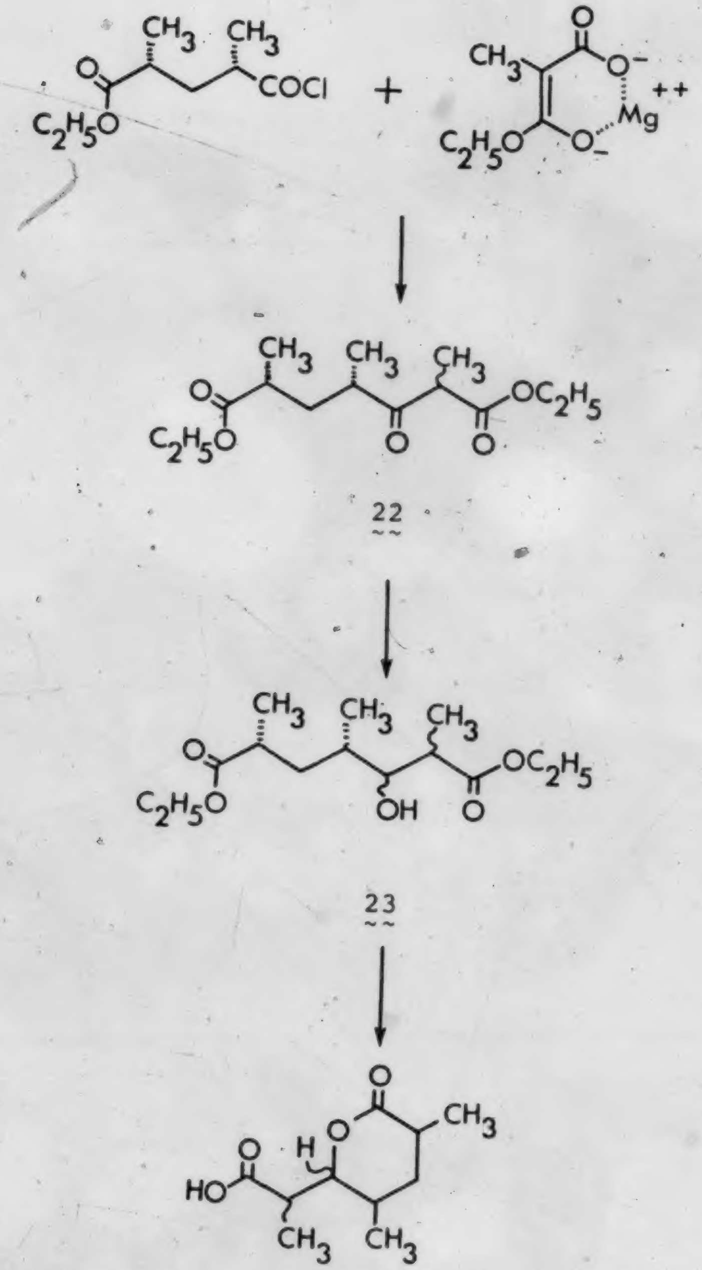


20

(-)-S-21

In 1963 Bergel'son and Batrakov[94a] reported a synthesis of the racemate of the Djerassi-Prelog lactonic acid. Their synthesis is outlined in Figure 8. Compound 22 was obtained in a straightforward manner starting with *meso*-α,α'-dimethylglutaric acid. Reduction of the ketone to give alcohol 23 was accomplished by several methods. These included hydrogen over Raney Nickel or chromium-nickel catalysts, triethoxyaluminum hydride, and lithium aluminum hydride. Saponification of the compound obtained from the latter reduction, followed by acidification gave a lactonic acid 24 in 58% yield which the authors stated was the

Figure 8: Russian Attempt at Synthesis of (±)-6


CH3
CH3
COCl
C2H5O
+
CH3
O
O−
Mg
++
C2H5O
O−
OC2H5
OH
HO
H
CH3

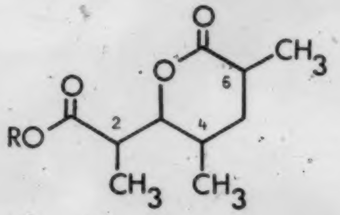
22

23

24

racemic form of the Djerassi-Prelog lactonic acid 6. Based on pmr and degradative studies of their synthetic material, the Russian workers concluded that the C_2 and C_3 configurations were S and R, respectively.

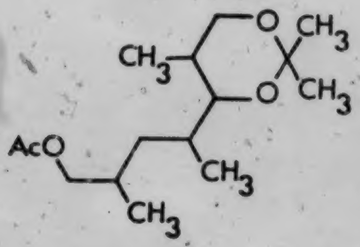
Because the assignment of Bergel'son and Batrakov was opposite to that predicted by Celmer's model, and because the identity of the synthetic lactonic acid was based solely on solution ir spectral comparisons, Rickards and Smith reinvestigated the problem in 1970.[91] They used pmr analysis extensively, as did the Russians, but authentic, rather than synthetic, lactonic acid (+)-6 was used for this renewed study.



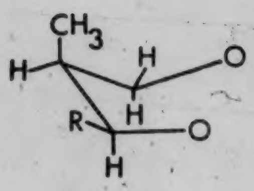
(+)-6 R = H

(+)-25 R = CH_3

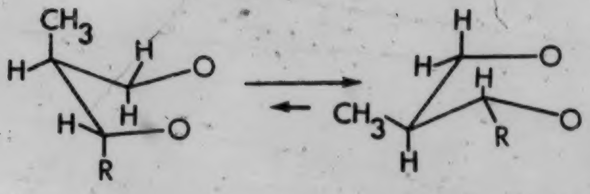
The vicinal coupling constant $J_{3,4}$ is 10 Hz in both the lactonic acid and its methyl ester 25. On this basis, Rickards and Smith concluded that H_3 and H_4 are anti-periplanar and thus C_3 has the S configuration. This assignment agrees with Celmer's model for macrolide stereochemistry. In order to study the configuration at C_2, **25** was converted into **26** by a series of reduction, ketalization and acetylation. This new compound had C_2 incorporated into its 1,3-dioxolane ring. The vicinal coupling constants between the C_2 proton and its three neighbouring protons were all small (less than 2.5 Hz). Based on this observation, the authors stated that this proton was *syn*-clinal to all three vicinal protons. Of the two structural orientations, **26a** and **26b** consistent with this conclusion, the latter was eliminated as conformationally unrealistic. The stereochemistry of C_2 is therefore *R*. The assignment of the *R* configuration to C_2 is in agreement with Celmer's model.



26



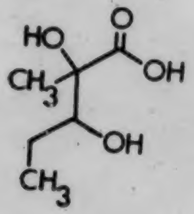
26a



26b **26c**

In the light of Rickards and Smith's evidence, it must by concluded that Bergel'son and Batrakov erred in assigning their synthetic lactonic acid as the racemate of (+)-6.* It is not possible to state at which point the Russian workers were misled. However, there are several reactions in their scheme which can cause epimerization of some chiral centres. For instance, the basic ester hydrolysis may have epimerized the C_2 centre.

Only the stereochemistry of the double bond and the configurations of C_{10} and C_{11} in methymycin remained undetermined. The pmr spectrum of methymycin established that the double bond had the E configuration, while ozonolysis of the antibiotic led to the isolation of C_{10} and C_{11} as (+)-2,3-dihydroxy-2-methylpentanoic acid.[91b] Compound 27



(+)-27

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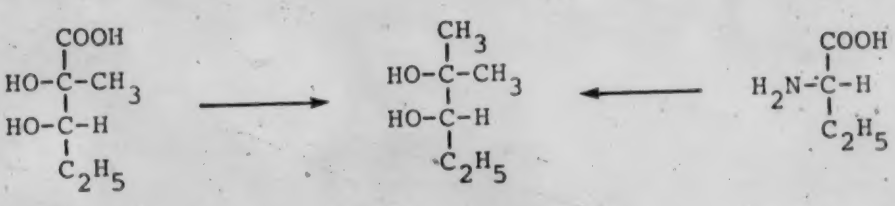
[*] Close inspection shows that the ir spectrum of 24 is very similar to that of the natural lactonic acid, but is not superimposable. The ir spectra of synthetic (±)-6 (this thesis) and authentic (+)-6 are exactly superimposable.

was identified as the *erythro* isomer by comparison with authentic racemic **27**. Final definition of the chirality at C_{10} and C_{11} as *S* and *R*, respectively, was possible when (-)-*erythro*-**27** was correlated through **28** with (+)-*S*-butyrine **29**.



(-)-**27** **28** **29**

Thus, through the efforts of Djerassi and his coworkers, and of Rickards and Smith, the total structure of methymycin has been determined. The stereochemistry of this macrolide is summarized in Table 3.

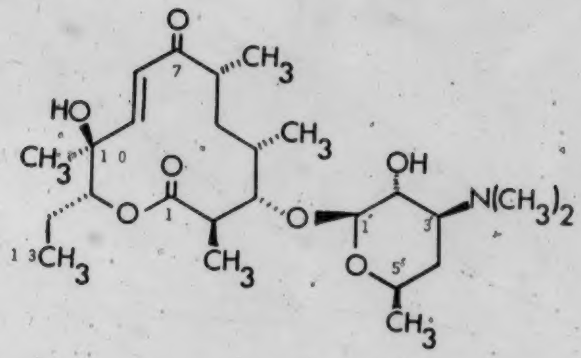
Table 3: Chirality of Methymycin

Carbon	Chirality
1	A
2	R
3	S
4	S
5	A
6	R
7	A
8	A
9	A
10	S
11	R
12	A
13	A
8-9	(E)-bond

Carbon	Chirality
1'	S (β-glycoside)
2'	R
3'	S
4'	A
5'	R

A = Achiral

R, S = Absolute Sense


O
7
CH3
HO
CH3
10
CH3
O
1
OH
N(CH3)2
O
1'
3'
13CH3
CH3
O
5'
CH3

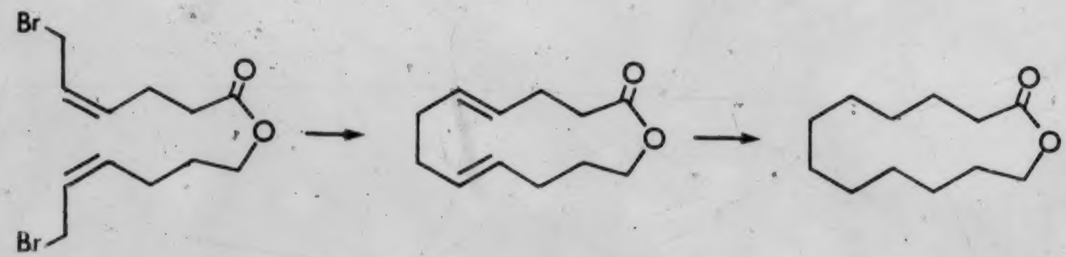
CHAPTER 3

PREVIOUS SYNTHETIC STUDIES OF MACROLIDES

There are four principal approaches to the synthesis of macrocyclic lactones: (1) the Baeyer-Villiger oxidation of the corresponding cyclic ketone,[95] (2) cyclization of the termini of an appropriately substituted ester, (3) peracid oxidation of a bicyclic enol ether precursor and (4) direct lactonization of a hydroxy carboxylic acid.

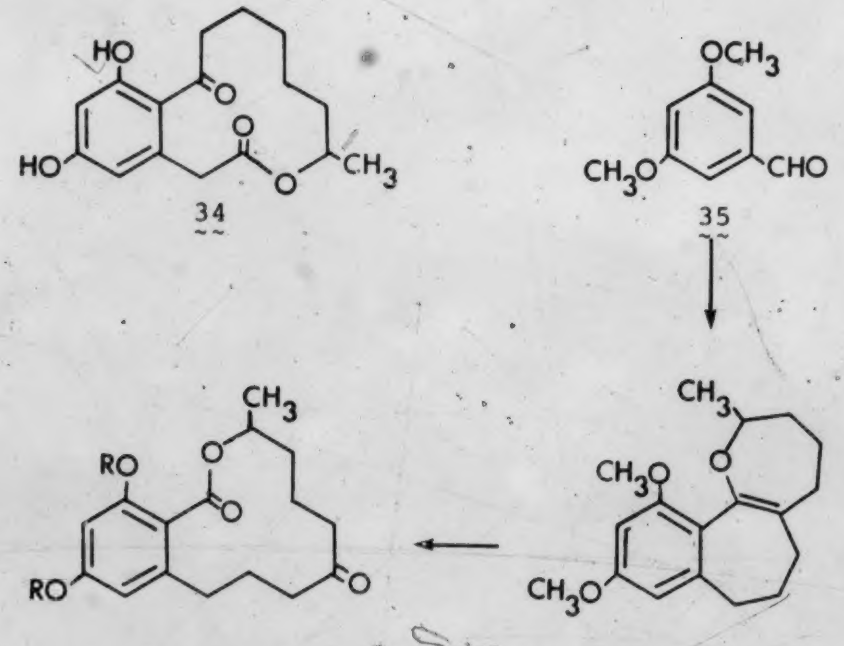
The first method is impractical for several reasons. The preparation of an appropriately substituted medium or large cyclic ketone would be just as, or even more difficult than the synthesis of the lactone itself. The ketone synthesis would have to be carried out under essentially neutral conditions in order that there is no chance of epimerization of any centres adjacent to the existing carbonyl functions, since the stereochemical integrity of the molecule must be preserved. Unfortunately, neutral methods for the preparation of ketones are very few in number. There is a further complication since the Baeyer-Villiger reaction would have to be selective as to which substituent of the ketone migrates.

In the late 1960's Corey made use of nickel(0) carbonyl to cyclize an allylic dibromide as part of the synthesis of the sesquiterpene humulene.[96] This carbon-carbon bond formation was later extended to the synthesis of a medium-ring lactone.[97] Reaction of compound 30 with nickel(0) carbonyl gave a 70-75% yield of diene lactone 31 which was subsequently hydrogenated to produce the thirteen-membered lactone 32. This reaction is also unlikely to be synthetically useful for the preparation of highly substituted lactones because of the difficulty in obtaining the properly substituted allylic termini, and because of the problems associated with further conversion of the diene into a highly functionalized macrolide.



30 31 32

The third method of approaching the problem has been used by Bagli and Immer[98] to synthesize 33, a structural isomer of curvalin 34. They used the oxidative cleavage method developed by Borowitz and Gonis[99] to ring expand the tricyclic vinyl ether 36 which yielded 37. Removal of the O-methyl groups afforded 33.



34

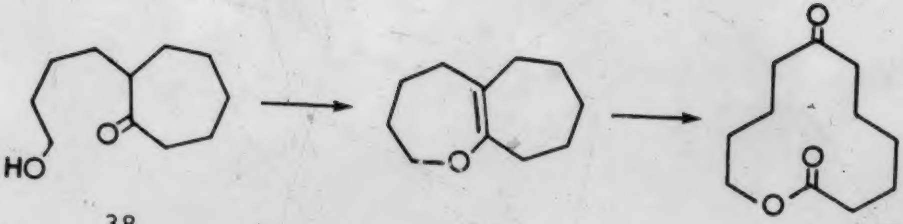
35

36

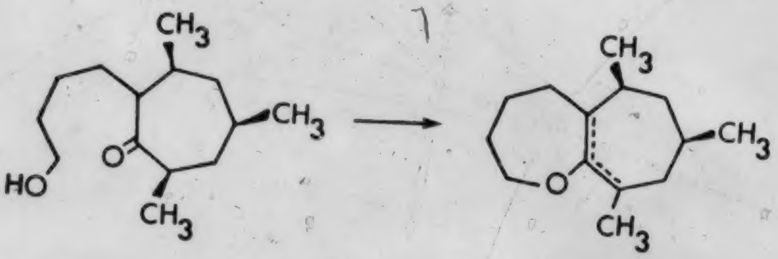
33 R = H

37 R = CH_3

More recently, Borowitz and coworkers[100] extended their method to determine the feasibility of using this type of cleavage to generate the methymycin lactone system. Their initial investigations involved the synthesis of 7-oxoundecanolide **40**.[101] Alkylation of cycloheptanone with a difunctional reagent yielded **38** after conversion of the free terminus of the alkyl side chain into a hydroxy group. Acid catalysed dehydration led to the vinyl ether **39** but only in low yields (15%).



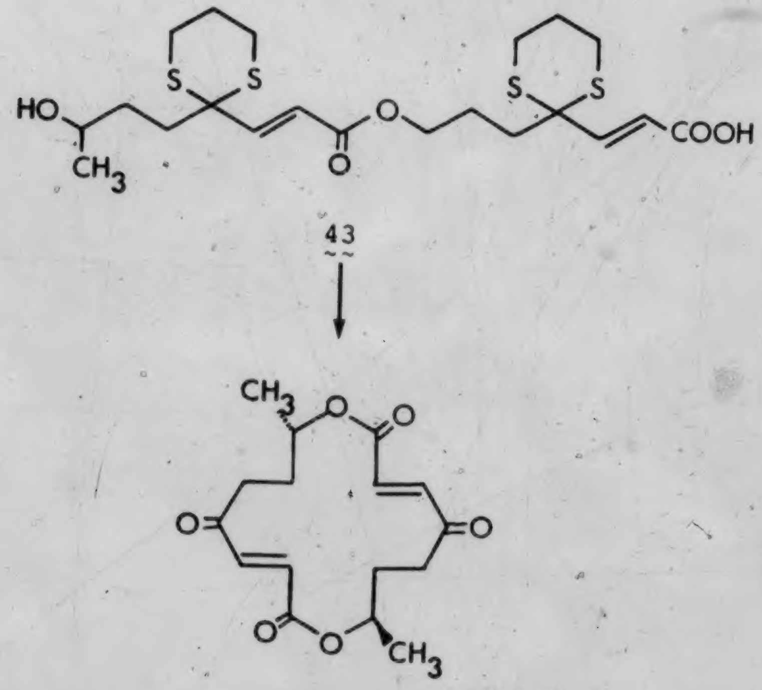
38 39 40



41 42

The cyclization reaction was found to produce even poorer yields if the starting ketone carried substituents. Thus, in the case of 41 cyclization "occurred to a minor extent" affording a mixture of isomeric enol ethers 42. The authors concluded that the present synthesis of cyclic vinyl ethers cannot be applied to the preparation of complex macrolides.

Cyclization of the corresponding hydroxy carboxylic acid[102] as a lactone synthesis has met with the greatest success. For instance, Colvin, Raphael and others[103] have reported the first synthesis of a non-aromatic macrolide, (±)-pyrenophorin 44. Compound 43 was prepared using classical methods and was converted into the acyl imidazolide and subsequently cyclized with base to give a 60% yield of a 1:1 mixture of diastereoisomers.



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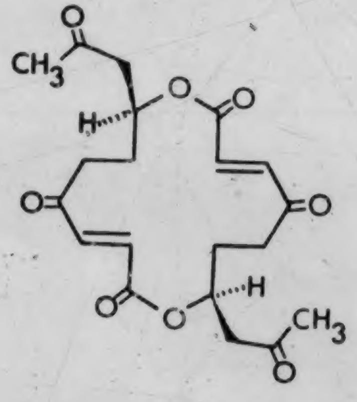
44

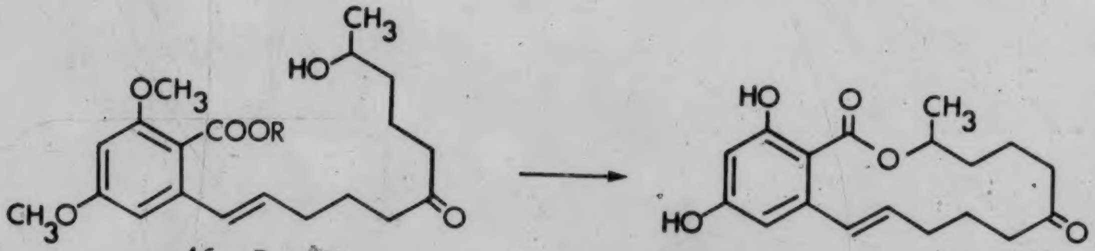
After hydrolysis of the thioketals, and removal of the *meso* product, (±)-pyrenophorin **44** was obtained. In this synthesis, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) was used to remove a 4-toluenesulphonylethyl protecting group. The use of a powerful reagent like DBN may destroy those labile groups normally present in more complicated macrolides such as methymycin and thus not allow this route to be generalized. More recently, a related compound

(±)-vermiculine 45, was synthesized by Corey *et al.*[104] using an efficient lactonization step which is discussed later in some detail.



45

Several successful syntheses[115] of the fourteen-membered pseudomacrolide zearalenone 48 have appeared in the literature. In two of these reports,[105a,c] the final steps involved a low yield (10%) lactonization of 46, catalysed by trifluoroacetic acid anhydride followed by cleavage of the *O*-methyl ethers. Another lactonization yielding zearalenone was carried out by cyclizing the hydroxy and methyl ester groups of 47 *via* an ester exchange using potassium *tert*-amylate.[105b]

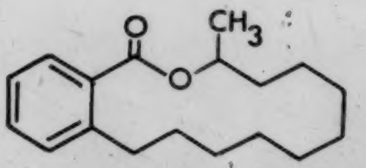


46 R = H

47 R = CH_3.

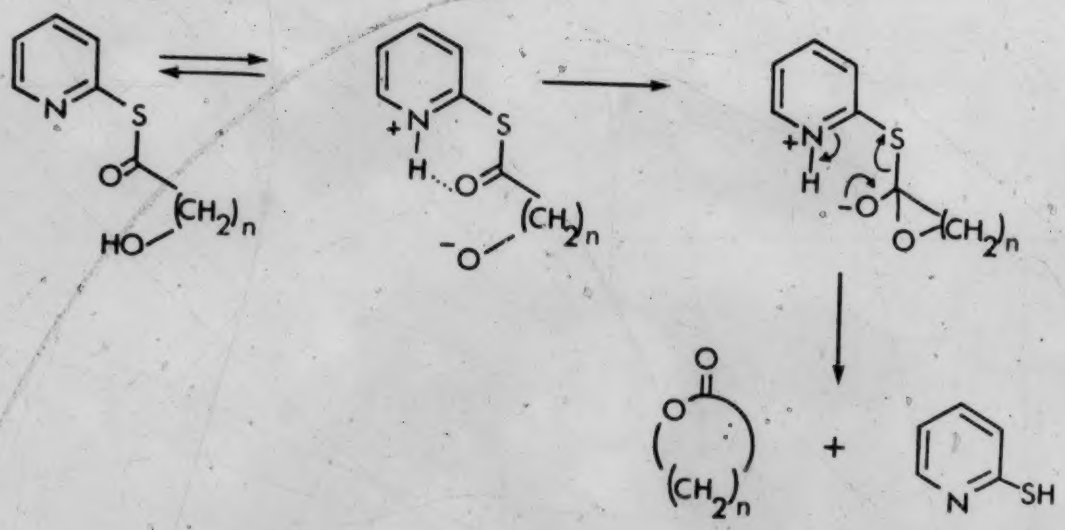
48

A synthesis of racemic dideoxyzearalane 49 has also been reported.[106] In this case the final lactonization was accomplished in 25% yield by using phosgene and triethylamine in dilute benzene solution.



49

The direct lactonization procedure appears to be the best approach to the synthesis of macrolides, however the yield needs improvement. At the time we announced our method (described in this thesis) at the 9th IUPAC meeting, Corey published a newer approach to this problem. He suggested activating the hydroxy and carboxy groups of the lactone precursor towards mutual reaction in order to improve the yield of lactonization. One way to activate both the hydroxy and carboxy groups would be to use a carboxylic acid derivative which would favour proton transfer from hydroxy to carboxy oxygen. Corey proposed the use of the pyridine-2-thiol ester, a functional group used by Mukaiyama[107] in his studies on peptide bond formation, as the activating group. A mechanism for the lactonization mechanism suggested by Corey is given in the following scheme. This electrostatically driven



reaction, if it indeed operates as shown above, could also proceed intermolecularly, but this problem should be overcome by using high dilution techniques.

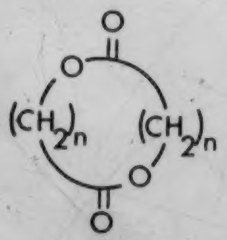
Corey proved his hypothesis by successfully lactonizing several aliphatic ω-hydroxy carboxylic acids, after first activating their carboxy functions by converting them into the corresponding pyridine-2-thiol esters. The cyclization reaction involved prolonged refluxing in the indicated solvents. The results are given in Table 4.

Table 4: Lactonization of ω-Hydroxy Carboxlic Acids[105d]

$HO(CH_2)_nCOOH \longrightarrow$ lactone

n	Solvent (Reaction time)	Ring Size	Yield glpc	Yield Isolated
5	benzene (10 hr)	7	87	71
7	xylenes (30 hr)	9	25	8
10	xylenes (20 hr)	12	64	47
11	xylenes (10 hr)	13	76	66
12	xylenes (10 hr)	14	79	68
14	xylenes (10 hr)	16	88	80

Along with the indicated amount of lactone formed in the reaction there was a variable yield of diolide 50 isolated. This product was a minor constituent (5-7%) except in the formation of the nine- and twelve-membered lactones where it accounted for 41 and 30% of the product, respectively.



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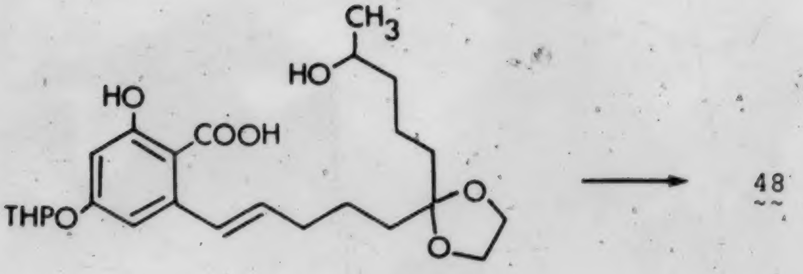
Corey applied this lactonization procedure to the synthesis of zearalenone.[105d] Cyclization of 51 with subsequent removal of the protecting groups gave the pseudomacrolide in 75% yield.



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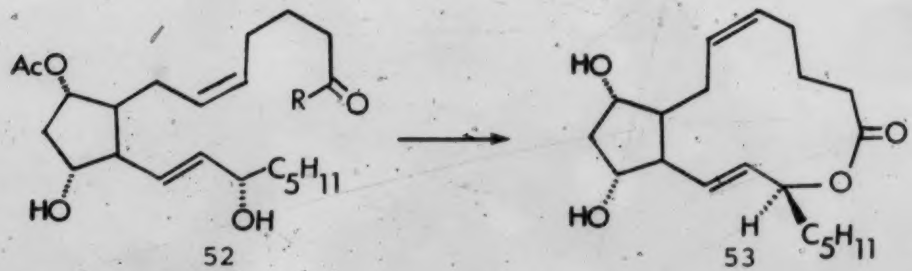
The use of this activation procedure has been extended to the synthesis of macrocyclic lactones in the prostaglandin series.[108] For instance 53 was obtained, following deacylation, in 67% yield by refluxing a xylene solution of 52 for thirty hours.

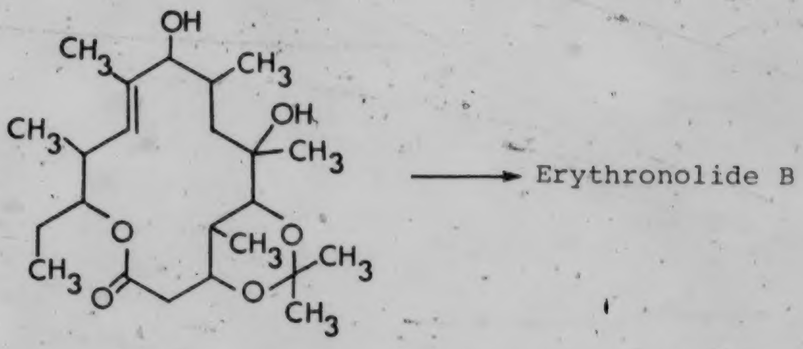


52

53

R = Pyridine-2-thiol ester

Partial syntheses of brefeldin A, carpaine, vertaline and erythronolide B were recently reported[109] while our manuscript was in press. This latter compound is of great interest since it is an authentic macrolide. Treatment of the seco-acid (the lactone ring opened, hydroxy acid, precursor) of 54, obtained by conversion of naturally derived erythromycin B, in tetrahydrofuran with two equivalents of 2,2'-dipyridyl disulphide and two



54

equivalents of triphenylphosphine for 22 hours at 25° led to the corresponding pyridine-2-thiol ester which could be isolated in 88% yield, and which upon heating at reflux in xylene for 72 hours afforded the macrocyclic lactone 54 in an unspecified yield. This compound was then converted into erythronolide B by a multistep process. The overall yield for the partial synthesis was not given, nor was any mention made of possible epimeric products.

Somewhat later, H. Gerlach[110] reported an improved cyclization method using the pyridine-2-thiol ester. Use of silver(I) salts to catalyse the reaction results in rapid formation of macrocyclic lactones and esters at room temperature under non-basic conditions. The yields are 70-85% for this reaction.

A synthesis of a macrocyclic thiene involving the use of a repeatable 2,3-sigmatropic shift as a ring growing reaction has also been reported.[111] The authors note that they are exploring extensions of this concept to carbocycle synthesis by sulphur extrusion, and toward the synthesis of macrocyclic lactones and lactams.

CHAPTER 4

A SYNTHETIC APPROACH TOWARDS METHYMYCIN

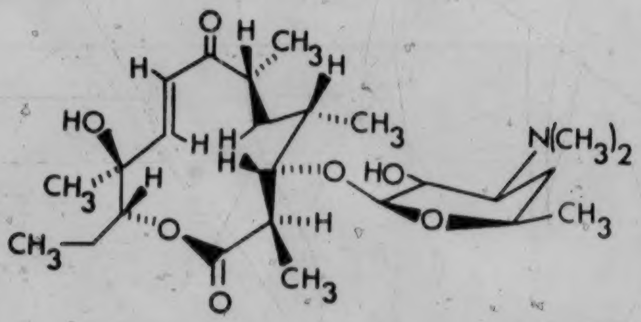
In the preceding chapters the properties of the macrolide antibiotics have been discussed. The most interesting aspect of the macrolides from the organic chemist's point of view is probably the common stereochemistry shared by the macrolide aglycones. We were fascinated with this structural feature, and at the time that we initiated this project approximately five years ago, it was not even clear how to approach the synthesis of this type of compound. By 1970, organic chemists had explored the area of natural product chemistry so extensively that general approaches for syntheses of most of the important groups of compounds, including steroids, terpenes and alkaloids, were available. In the field of antibiotics, total syntheses of penicillins and cephalosporins, and tetracyclins were already completed, and the only remaining main family of antibiotics which challenged us was the macrolide antibiotics, for reasons which are rather obvious from the preceding discussions. We hoped that a successful synthesis of one member of the macrolide family would lead to a general synthetic approach to other members of the group. Needless to say, such a scheme would also be valuable for biochemical studies of the macrolides as well as of general importance in synthetic organic chemistry.

There are two main problems associated with the synthesis of the macrolide antibiotics. They are: (1) the stepwise stereospecific introduction of each chiral centre preferably via an aldol or Claisen type condensation and (2) the formation of the lactone ring. In light of Stoll's earlier work, a twelve-membered lactone should be the hardest to cyclize. We reasoned that if we were successful in cyclizing this medium ring system, then we were confident that the larger fourteen- and sixteen-membered rings would also prove amenable to cyclization (vide infra). We therefore felt that our first priority was to establish the feasibility of the lactonization step before attacking the problem of a stereospecific stepwise synthesis. The simplest of the nonpolyene macrolides, methymycin, was chosen as the first goal of our synthesis. Methymycin, being the smallest member of the macrolide family, had the advantage that the stereochemical problems associated with the ring system are minimal. Thus, while the construction of the seco-acid is presumably easiest of all, the lactone ring formation would present difficult problems. In particular, the three inner hydrogens discussed below, further complicated this problem. Therefore, methymycin or methynolide is the best compound for the purpose of testing our approach.

Before our initiation of this project two approaches to the synthesis of large-ring lactones had been tested as discussed in Chapter 3. Borowitz concluded that his enol ether cleavage approach, although useful for the synthesis of relatively simple lactones, was of no use in the synthesis of the highly substituted macrolide aglycones. The other method, again as examined earlier, appeared impractical for our purpose.

The more obvious but extremely risky approach would be the cyclization of an appropriately substituted long chain compound. When this project was begun in 1970, there were no efficient methods for the synthesis of large ring compounds. For instance, the cyclization of the relatively simple lactone zearalenone was proceeding in only about 10%, and in light of Stoll's experiments this was generally thought to be about the highest yield that could be hoped for. However, we believed that in view of the conformational rigidity of the macrolide aglycones that cyclization would proceed in much higher yields than with the aliphatic compounds studied by Stoll.

In Chapter 1 Section E, the conformational rigidity of erythronolide B was discussed. This lack of flexibility in the aglycone is also present in methymycin. A conformational analysis based mainly on the CPK atomic model of methymycin and partially on a pmr analysis suggested that methymycin most likely has the conformation indicated below.

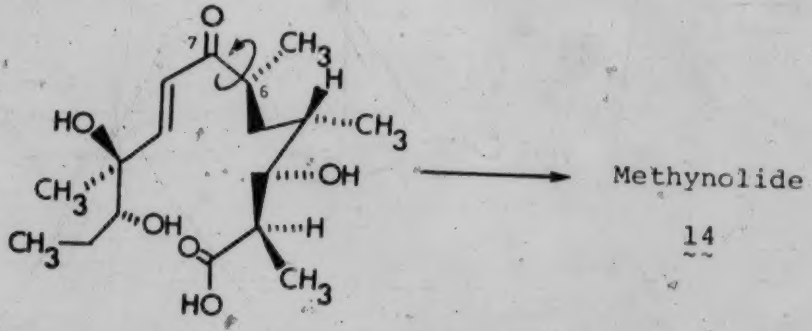


The molecule is quite rigid and conformationally fixed as evidenced by physical data and as judged from the model, which can hardly be twisted once the lactone ring has been constructed. The three hydrogen atoms located inside the ring are on different planes, and thus the van der Waals repulsion which might be expected if methymycin were essentially planar is to a large extent removed in the actual conformation. This van der Waals repulsion is further reduced as one goes to the larger lactones, and at the sixteen-membered ring is almost totally absent. Because of this trend, we believed that the aglycones of the larger macrolides should be even easier to form than that of methymycin. The desosamine residue further strengthens the conformational rigidity of the whole system.

This lack of flexibility is also extended to the seco-acid 55 of the methymycin aglycone. Because of the presence of the α,β-unsaturated ketone and more importantly the substituents along the chain, rotation of the C_6-C_7

single bond is the only extra degree of freedom allowed in the seco-acid. Thus, rotation about this bond

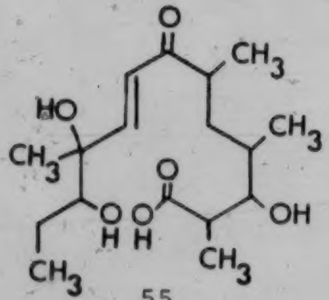
55



14

automatically brings the hydroxy group at C_{11} close to the C_1 carboxy group, and lactone formation may compete favourably with intermolecular condensations.

Therefore, based on this conformational analysis, if we can construct a suitably substituted hydroxy carboxylic acid or its equivalent, we have reasoned that there is a good chance that lactonization to yield methynolide may be effected. Two possible immediate precursors (55 and 56) to the lactone ring are shown below.



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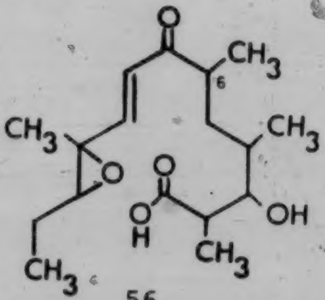
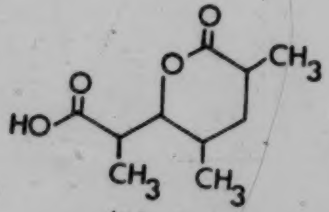


56

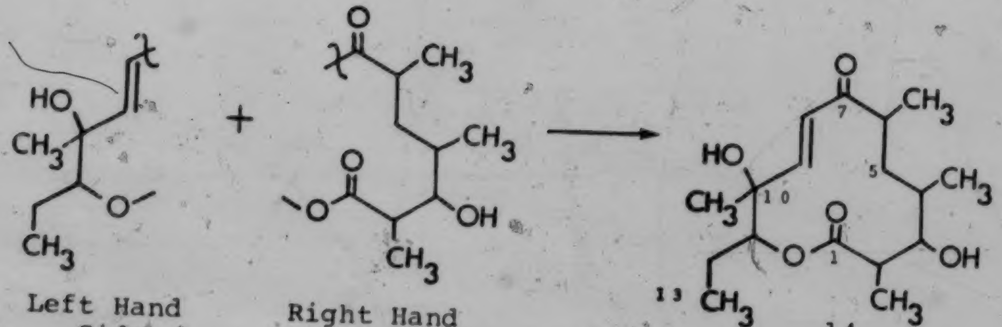
Lactonization from 56 may proceed with or without the assistance of a Lewis acid, and with care, a Lewis acid should not epimerize the C_6-methyl group. Once the synthesis of the aglycone has been accomplished, the remaining task only involves attachment of desosamine to the secondary hydroxy group of methynolide.

Unfortunately, the limited world supply of natural methymycin (<400 mg) prevented us from degradation of methynolide to produce 55 and 56 or their equivalent, which could have been used to test the feasibility of this lactonization approach. We therefore have been forced to proceed with a totally synthetic route without the benefit of a preliminary relay study, a risk which we considered worth taking.

Djerassi reported (see Chapter 2) that upon degradation, methynolide yields (+)-6. This lactonic acid incorporates C$_1$ through C$_7$ of methynolide, the segment which we refer to as the right hand side of the molecule.



(+)-6



Left Hand Side

Right Hand Side

14

We call the remaining C_8 through C_{13} fragment the left hand side. Our synthetic plan involved the preparation of the left and right hand sides of methynolide, condensation of these fragments to give 55, 56 or their equivalent, followed by cyclization to form methynolide 14.

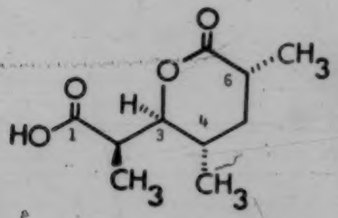
Our ultimate goal is the synthesis of the natural form of methymycin, and thus we need to either use optically pure reagents throughout the synthesis or carry out the reactions in such a way that resolution or an asymmetric synthesis can be accomplished at some stage. There are at least three ways to combine two stereochemically matched components. First, both segments are resolved or asymmetrically synthesized and combined, second, transmit the stereochemical information of one segment to the other, and third, one segment is resolved and used to resolve the other molecule. Although the second method is most attractive and is currently being explored, we decided to use the latter method in the synthesis of methymycin.

With the assumption, which later proved to be valid, that the wrong pair of isomers would not cyclize or at least not cyclize as efficiently as the correct pair, we proceeded with our synthesis. Racemic Djerassi-Prelog lactonic acid (±)-6 appeared to be an ideal intermediate in the synthesis. Not only would the successful preparation of (±)-**6** complete the right hand portion of the cyclization precursor, but the chemically non-equivalent carboxy groups, a free acid and a δ-lactone, should allow fixture of the simpler left hand portion specifically to the desired group. The smaller left hand fragment of the precursor can be more easily prepared in optically active form than can the lactonic acid, ~~and th~~erefore will serve as a resolving agent for the right hand side of methynolide during the lactonization, since the conformational analysis, based on the CPK model, indicated that only the correct precursor will cyclize. In addition, the correctness of the relative stereochemistry in the synthetic lactonic acid can easily by checked by comparing it with naturally derived (+)-**6**.

CHAPTER 5

A SYNTHESIS OF THE RACEMIC DJERASSI-PRELOG LACTONIC ACID

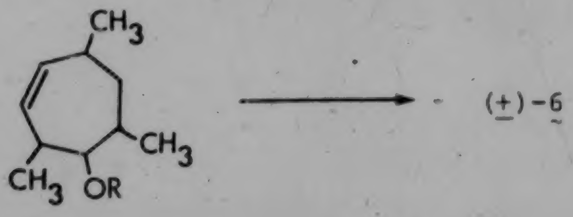
An efficient synthesis of the Djerassi-Prelog lactonic acid (±)-6 necessarily involves the introduction of four asymmetric centres in a highly stereoselective manner. K. E. Wilson in conjunction with C. Kim and H. Davis was able to isolate a few milligrams of the racemic lactonic acid. His pioneering work is fully described in his thesis.[64] In order that the synthesis of methymycin could be continued as outlined above, the reaction sequence used by Wilson had to be improved considerably.



(±)-6

As noted previously, our ultimate aim is to construct the methymycin aglycone in a stereospecific stepwise manner. However, at this stage of the investigation it is more important to establish the feasibility of the final lactonization to produce methynolide before attempting to improve the synthetic scheme. We thus first proceeded with a more conventional synthesis of methynolide seco-acid.

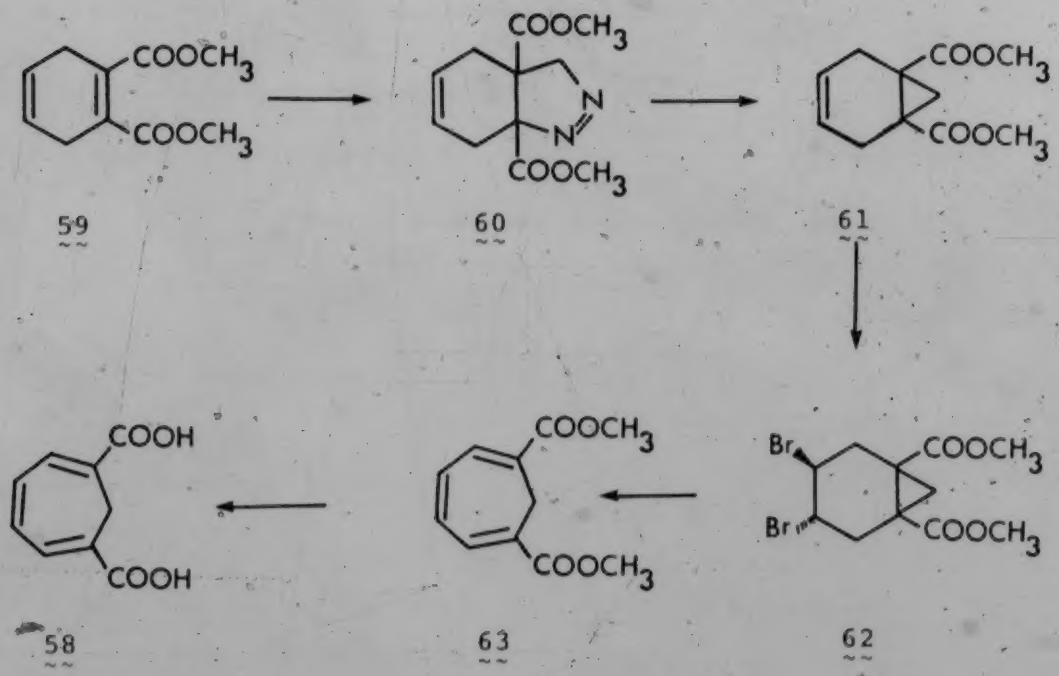
The generation of asymmetric centres in a stereoselective fashion is much easier to accomplish in a cyclic structure which possesses some rigidity than in a flexible acyclic analogue. After introduction of the required asymmetric centres, cleavage of the ring would afford suitable precursors for (±)-6. The trimethylcycloheptenol derivative 57 was selected by Wilson as the key synthetic intermediate.



57

Cleavage of the double-bond in an oxidative manner, followed by removal of the hydroxy protecting group, should lead directly to (±)-6.

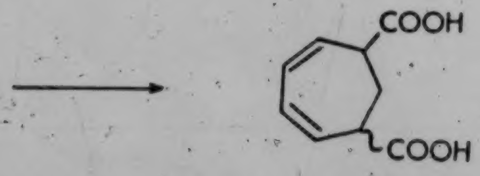
In Wilson's synthetic route 3,5,7-cycloheptatriene-1,3-dicarboxylic acid 58 was chosen as the starting material for preparation of 57. This diacid had been previously synthesized by two research groups.[112] The more recent route published by Vogel[112b] and outlined in the following scheme was used by Wilson.


COOCH3
COOCH3
59
COOCH3
N
N
COOCH3
60
COOCH3
COOCH3
61
Br
Br
COOCH3
COOCH3
62
COOCH3
COOCH3
63
COOH
COOH
58

The reaction sequence to obtain 58 involved some problems in a large scale operation. The addition of diazomethane to the Diels-Alder adduct 59 is not very efficient and requires several treatments with fresh diazomethane over a one-week period. Thus, the reaction mixture often contained as much as one mole of potentially explosive diazomethane. In addition, the photolysis of pyrazoline 60 had to be carried out on small amounts of material (<5 g) in order to produce a clean product in high yield. Nevertheless, this procedure was initially followed.

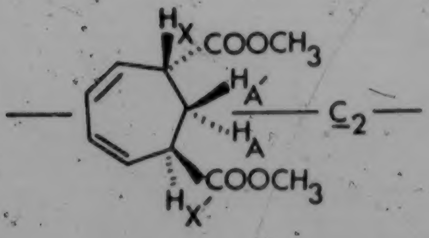
Since the carboxy groups of 58 were ultimately intended to be transformed into the two methyl groups at C_4 and C_6 of (±)-6, it was necessary that these groups have a *cis* orientation in subsequent products. Reduction of 58 with sodium amalgam[113] provided a high yield of the desired diacid 64. The product consisted of 90% of the *cis* isomer. This product distribution is in marked contrast to the reduction of phthalic acid which yields virtually only the *trans* isomer.[113b,c]

58

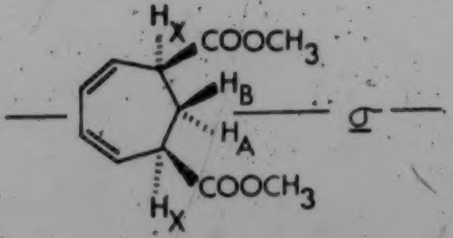


64

The isomeric purity of 64 was established by a pmr study of the dimethyl esters of 64. The pmr spectra of the *cis* and *trans* diesters, are expected to be quite different. In the *trans* diester 65, there is a two-fold



65



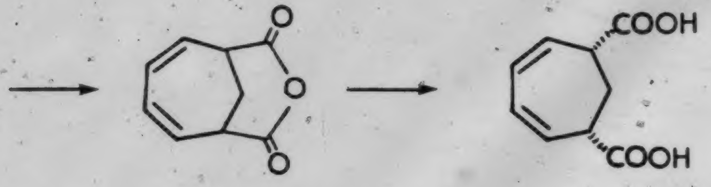
66

rotation axis (C_2) through the methylene group necessitating the chemical equivalence of the geminal protons on C_2. Thus, the methylene protons may be analysed as the AA' part of an AA'XX' system. In general, this half of the nuclear spin system consists of twelve lines.[114] However, since the $J_{X,X'}$ coupling constant is expected to be approximately 0 Hz, the AA' pattern reduces to six lines. Experimentally, a triplet (τ 7.75, $J = 6$) was observed indicating that the *cis* and *trans* coupling constants are equal.

In contrast to **65**, the *cis* diester **66**, has a mirror plane (σ) through the methylene group and thus the two geminal protons on C_2 are not chemically equivalent. Thus, these two protons may be treated as the AB part of an ABX_2 spin system. Experimentally, there are observed twelve lines appearing as four off-centre triplets, in agreement with the prediction of an ABX_2 pattern.

The *cis* diacid was purified *via* its anhydride **67**. When the mixture **64** was heated for a short time in the presence of acetic anhydride, the cyclic anhydride **67** was obtained in 80% yield. The *cis* diacid **68** was then obtained by treatment of the anhydride with aqueous sodium bicarbonate.

64

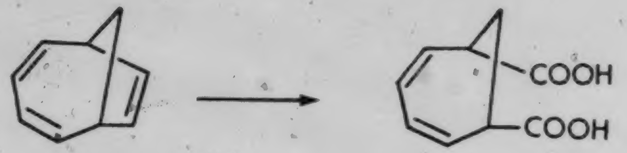


67

68

Our first task involved improving the yield of the cis diacid **68**. In collaboration with H. Davis and G. Spessard, an alternative and more efficient route to diacid **68** has been executed with a very gratifying result.

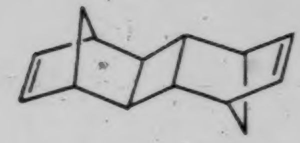
In 1966 Cannell[115] reported that bicyclo[4.2.1]nona-2,4,6-triene **69** is formed during the pyrolysis of the $[{}_{\pi}2_s + {}_{\pi}2_s]$ dimers of bicyclo[2.2.1]hepta-2,5-diene. If the isolated double bond of **69** could be selectively



69 **68**

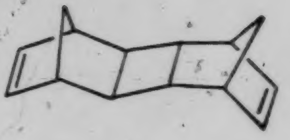
oxidized by cleavage of the C_7-C_8 bond, diacid **68** could be obtained directly.

Schrauzer[116] reported that bisfumaronitrile nickel(0)[117] dimerizes bicyclo[2.2.1]hepta-2,5-diene to give exclusively the anti-fused isomers **70**, **71** and **72**. The main product is **71** which is present as approximately 80% of the mixture. The original procedure involves a sealed tube reaction.[116a] When a large scale (350 g) reaction was carried out behind a safety shield, a violent explosion occurred which caused extensive damage



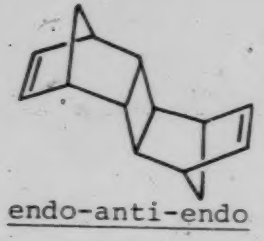
exo-anti-exo

70



exo-anti-endo

71

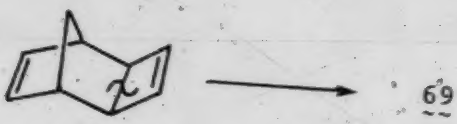


endo-anti-endo

72

to the fume hood in which the reaction was carried out. Subsequent reactions were then carried out in a sealed tube placed inside a heavy-walled stainless steel hydrogenation apparatus.

Pyrolysis of the mixture of the dimers in a flow system, followed by distillation of the product, provided 69 in 75-80% yield. The pyrolysis occurs over a wide temperature range (250-500°)[115] and the product distribution is a function of temperature, contact time and surface area. If too low a temperature is used, imcomplete cracking occurs, resulting in some exo-tricyclo[4.2.1.0^{2,5}]-nona-3,7-diene 73, a pyrolysis intermediate, along with a considerable amount of uncracked dimer. Too high a temperature or too long a contact time results in considerable aromatic material being produced because of further

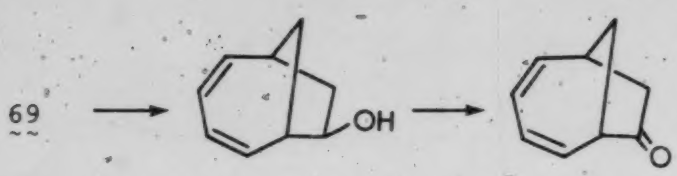


73

69

reactions of 69 in the pyrolysis tube. In both cases there is usually some *exo-anti-exo* dimer 70 which is uncracked. This observation is consistent with Cannell's report of the reactivity of this isomer. The most convenient method of monitoring the pyrolysis is by removing an aliquot of pyrolysate and taking its pmr spectrum. The temperature and/or the flow rate (and thus the contact time) are varied until optimum conditions for the pyrolysis are obtained.

Hydroboration of 69 was chosen as the method of oxidizing the isolated double bond. This method has an advantage over other oxidation methods since the probability of skeletal rearrangement is extremely low during the reaction. Hydroboration was found to occur primarily at the cyclopentene double bond even though cycloheptene is hydroborated by bis(3-methyl-2-butyl)-borane five times faster than is cyclopentene.[118] This fact may be rationalized by noting that the reactivity of the diene moiety should be reduced somewhat because of conjugation.[119] In addition, molecular models indicated that the methylene bridge is inclined slightly towards the plane of the diene, providing some shielding from *exo* attack by the borane. Use of bis(3-methyl-2-butyl)borane[120] as the hydroborating agent produced alcohol 74 in 90% isomeric purity and in an overall yield of 75%. The hydroxy group was shown to be in the



74 75

exo configuration, as expected, by pmr shift studies. This aspect is elaborated on below.

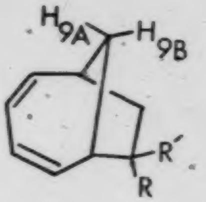
Oxidative cleavage of the C_7-C_8 bond of 74 first requires the introduction of functionality at C_8. In order to activate this position 74 was oxidized to ketone 75. Standard methods such as Sarett, Jones and Collins oxidations failed in this reaction probably due to skeletal rearrangements of the alcohol. The Oppenauer[121] method using aluminum *tert*-butoxide[122] and 4-benzoquinone proved satisfactory giving ketone 75 in up to 75% yield. More recently a chromate oxidation[123] applicable to a large scale operation appeared in the literature which also proved satisfactory for this reaction, although the yields are somewhat lower (40-50%).

Evidence for the *exo* orientation of the hydroxy function in 74 was provided by a pmr study of the effect of the lanthanide shift reagent, tris(1,1,1,2,2,3,3,-heptafluoro-7,7-dimethyl-4,6-octanedionato) europium(III), or more simply Eu(fod)$_3$, on 74 and on the *endo* isomer 76, produced by reduction of ketone 75 with lithium aluminum hydride. Carbon tetrachloride solutions of 74 (ca. 0.28M), containing various amounts of Eu(fod)$_3$ were examined by pmr spectroscopy. With the aid of decoupling experiments, complete proton assignment of the spectra was possible. A plot of the resulting proton chemical shifts (τ) versus the number of mole equivalents of shift reagent (C) showed a good linear relationship for $C \leq 0.3$. At higher concentrations of shift reagent, the chemical shifts slowly approached saturation. A similar experiment was carried out with endo isomer 76. Table 5 lists the slopes of the linear plots of the two bridging protons, H_{9A} and H_{9B}, in the two compounds.

Whereas the slopes for the bridging protons in 76 are approximately the same, this is not the case in 74. One of the bridging protons travels downfield twice as fast as the other. This behaviour is just that expected for the endo alcohol and the exo alcohol, respectively.

Hydroxymethylene derivative 77 was then prepared by conventional methods[124] from ketone 75. Subsequent oxidative cleavage with sodium metaperiodate according to a modified form of the method developed by Wolfram[125] provided an almost quantitative yield of diacid 68. The pmr spectrum of the dimethyl ester of the cleavage product showed no evidence of the trans isomer.

Table 5: Effect of Eu(fod)$_3$ on the Chemical Shifts of the Bridging Protons in 74 and 76



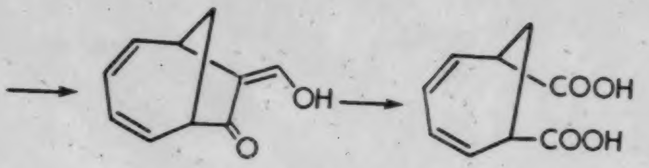
74 R = H, R' = OH

76 R = OH, R' = H

Cmpd	Δτ/C	
	H_{9A}	H_{9B}
74	-9.3 ± 0.3	-18 ± 2[a]
76	-5.6 ± 0.1	- 6.2 ± 0.1

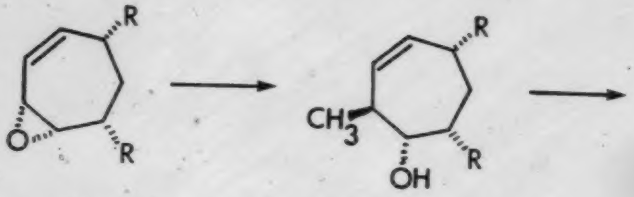
a) The larger error associated with the slope for H_{9B} in 74 arises from some uncertainty in the exact chemical shift of H_{9B} in the various spectra.

75



77 68

Having now achieved an efficient synthesis of diacid 68 which allows 200 g of this material to be obtained in less than four weeks, the next step in the preparation of 57 involves difunctionalization of one of the double bonds of 68. The opening of the *cis* monoepoxide 78 derived from 68 with a methylating agent would introduce the required *trans* related hydroxy and methyl groups of 57.

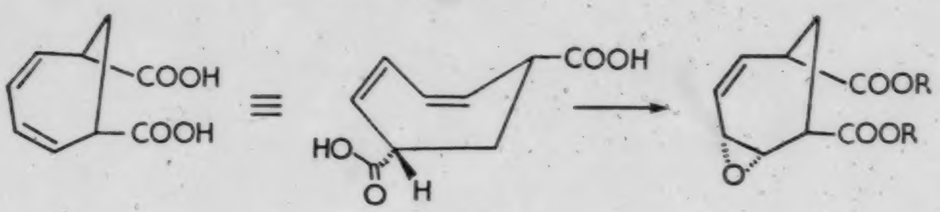


57

78 79

This conversion was performed using the method developed by Wilson and Kim and is fully described in Wilson's thesis. Their route is briefly described here for the sake of continuity.

After trying several approaches, it was found that introduction of the epoxide in the desired manner could be achieved only by direct epoxidation of diacid 68 with 3-chloroperbenzoic acid in a mixture of dichloromethane and tetrahydrofuran. The product ratio of *cis* and *trans* epoxides was approximately 7:3, a ratio somewhat improved compared with earlier results. The preference for the *cis* isomer indicates that there may have been some directing effect by the carboxy groups during the reaction. The product ratio was determined by examination of the pmr spectrum of the dimethyl esters of the epoxidation products.[64]



68

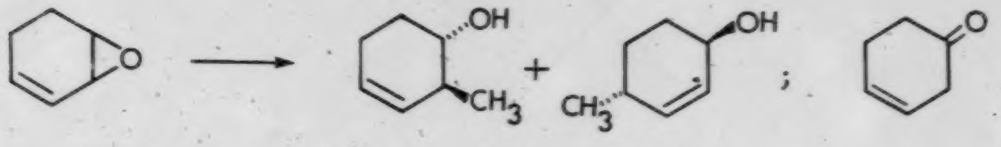
68a

80 R = H

81 R = CH_3

The directing effect of a carboxy group (rather than hydroxy[126a,b]), if it is indeed operating, is rarely precedented[126c,d] to the best of our knowledge. The effect may be rationalized by examining diagram 68a which more closely represents the geometry of the diacid based on molecular models than does 68. It can be seen that one of the carboxy groups is almost underneath the double bond which is epoxidized. It is possible that the peracid was directed to the underside of the double bond by hydrogen bonding with the nearby carboxy group.

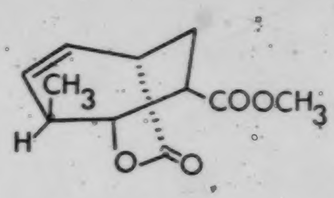
Lithium dimethylcuprate[127] was chosen over other methylating agents such as methylmagnesium chloride or dimethylmagnesium which attack allylic epoxides primarily in a 1,2 fashion[128] for the reaction with 80, because of the cuprate's inertness to the ester function and its assumed low basicity. The concurrent epimerization of one of the carboxy groups during opening of the epoxide would thus be minimized. Studies[129] done by C. Kim of our laboratory on the reactions of lithium dimethylcuprate with various allylic epoxides have shown that a significant amount of 1,2 attack by the transferring methyl group can occur. For instance, in the case of cyclohexene epoxide 82, 83 and 84 were obtained in roughly equal amounts with an overall yield of 85-90%. There was a



82 83 84 85

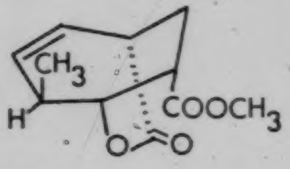
variable amount of 85 (0-23%) produced as the sole by-product of the reaction. In 80 the ring system is puckered, unlike the planar cyclohexene monoepoxide system of 82, and thus the double bond is expected to participate only to a small extent in the methylation reaction. Thus it was hoped that very little, if any, 1,4-allylic attack by the cuprate would occur during the opening of the epoxide in 80 with lithium dimethylcuprate.

Accordingly, diacid 68 was epoxidized as described above, and was converted, without purification, into the corresponding dimethyl ester 81 by treatment with diazomethane. The mixture of epoxy diesters was then directly added to a cold solution of lithium dimethylcuprate. The reaction was very rapid. Workup and isolation provided a crystalline lactone 86 (mp 65-68°) in an overall yield of 25-30% from diacid 68. During the reaction the alkoxide anion attacked the methyl ester to



86

provide the lactone directly. Strong evidence that lactone 86 had the indicated structure was provided by its pmr and ir spectra.[64] The possibility that the lactone might have structure 87 due to epimerization during the methylation reaction was ruled out by Wilson. Deuterium incorporation studies endorsed this point and also that lactone 86 with the carbomethoxy group in the pseudo-equatorial position was indeed the more stable isomer after all.



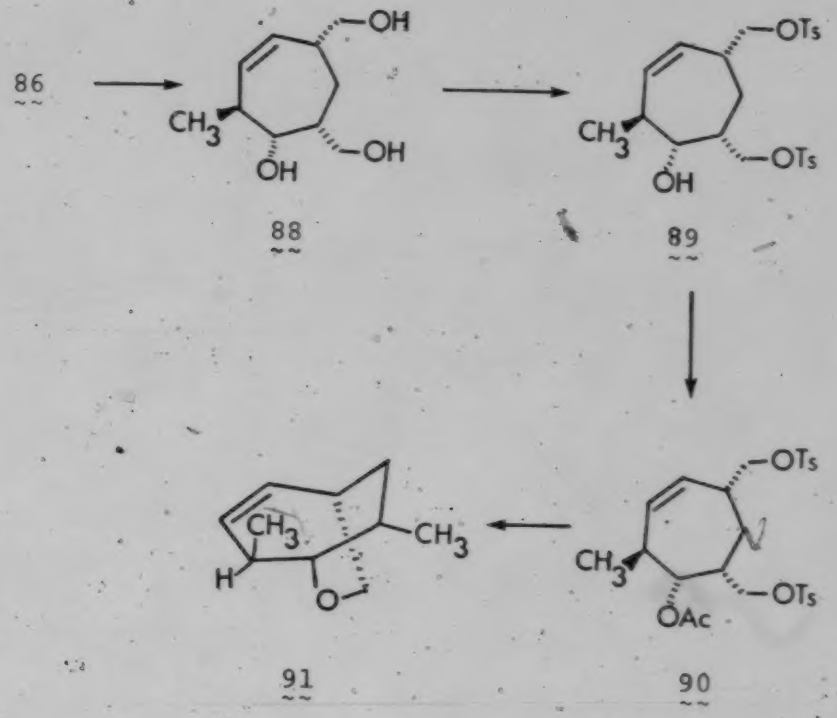
87

Lactone 86 was an important intermediate. All of the stereochemistry contained in 57 had now been introduced. The next step in the synthesis was the reduction of the carbomethoxy groups to methyl groups. The obvious methodology applicable to this conversion is indicated below.

$$RCOOR' \longrightarrow RCH_2OH \longrightarrow RCH_2X \longrightarrow RCH_3$$

X = sulphonate, halide, SR"

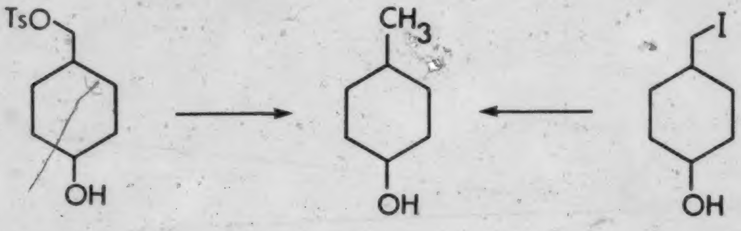
Reduction of 86 with lithium aluminum hydride proceeded smoothly to provide the corresponding trihydroxy compound 88. Subsequent treatment with two equivalents of 4-toluenesulphonyl chloride gave ditosyl alcohol **89**. In Wilson's synthesis **89** was converted into the crystalline ditosyl acetate **90** with acetic anhydride in pyridine. Direct lithium aluminum hydride reduction of **90** unfortunately led to formation of ether **91**.



It was obvious that a more selective and milder reducing agent was required for the conversion. At the time of Wilson's investigation, Hutchins *et al.*[130] reported that sodium cyanoborohydride in hexamethylphosphoric triamide was capable of reducing tosylates, bromides and iodides to the corresponding hydrocarbons under relatively mild conditions. The reported yields are excellent, often greater than 90%, and the reagent is inert to most of the other common functional groups (e.g. aldehyde, epoxide, ketone, ester and nitrile). The ease of the reduction follows the order of softness of the leaving group.

I > Br > OTs

Model studies carried out by G. Spessard with compound 92 prepared from 4-hydroxycyclohexane carboxylic 1,5-lactone[131] showed that forcing conditions were necessary (extended heating at 120°; poor yield) to convert

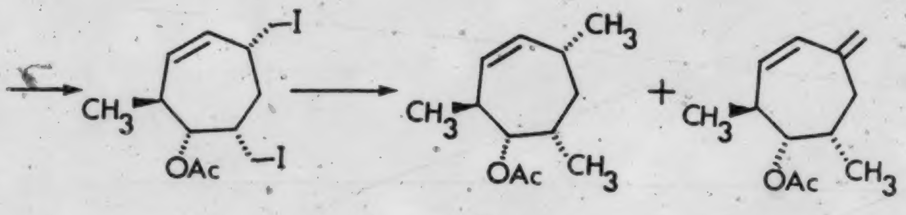


92 94 93

the tosylate into a methyl group. However, if the tosylate were converted into the corresponding iodide 93 the reaction proceeded under much gentler conditions. This result is in accord with Pearson's Hard and Soft Acid-Base Principle,[132] since iodide and hydride are both soft bases.

On the basis of this model study, 90 was converted into diiodide 95 by using lithium iodide in acetonitrile in the presence of mercury[133] (to remove any free iodine liberated), and was then treated with sodium cyanoborohydride. This reaction did indeed yield desired compound 96 but in a maximum of 25% based on lactone 86. However, the result was very often not reproducible and there was considerable dehydroiodination occurring during the reaction producing compound 97.

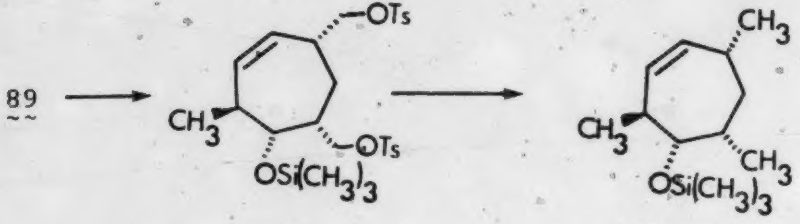
90



95 96 97

The overall conversion of lactone 86 into trimethylcycloheptenyl acetate 96 was proceeding in a barely acceptable yield, and we strongly felt that there was room for improvement. A more efficient reducing agent was required for the conversion of a sulphonate ester or halide into the corresponding hydrocarbon. We felt that this conversion represents one of the important processes in synthetic organic chemistry, and thus we devoted considerable time to discover a new methodology applicable to this conversion. Our investigations led to the development of a new cuprate reagent[134] which is discussed in detail in Part II of this thesis.

The free hydroxy group of 90 was first protected as the trimethylsilyl ether.* Treatment of 98 with lithium dihydrocuprate[134c] gave an 86% yield of reduced compound 99 along with 10% recovered tosylate-containing material after overnight stirring at room temperature.



98 99

By using the trimethylsilyl ether as a protecting group, 99, a compound equivalent to 96 can now be reproducibly obtained in up to 75% yield from lactone 86. This more than triples the yield obtained by Wilson's route and the working time required for this conversion is much less. This improvement in the synthesis has now provided an amount (25 g) of 99 sufficient for further conversion to the final product.

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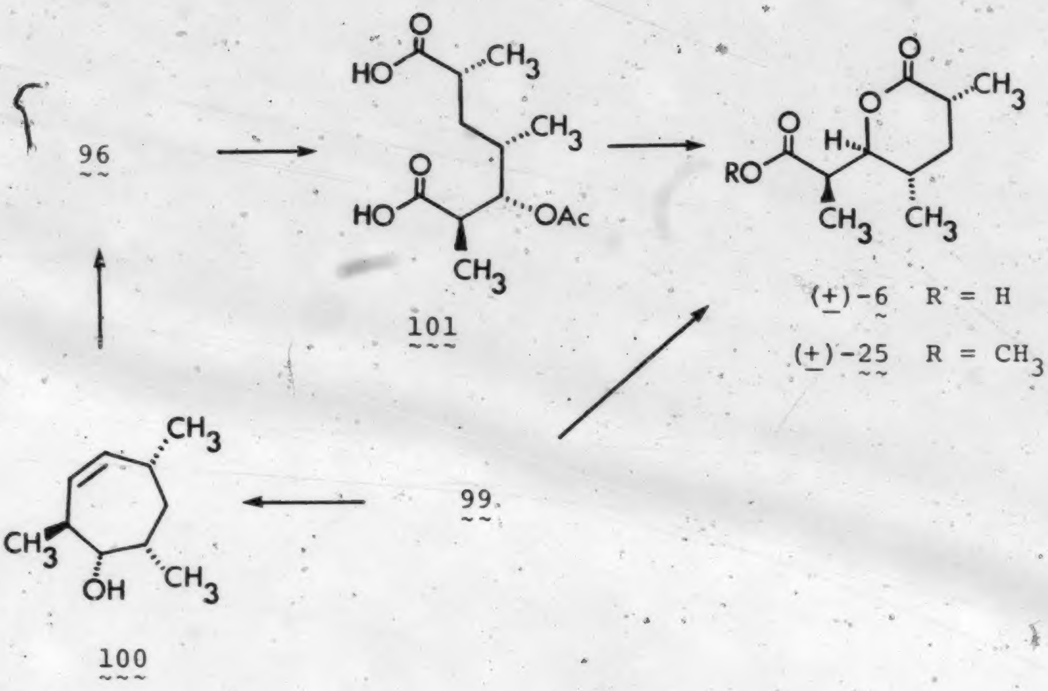
* When ditosyl acetate 90 was treated with the cuprate reagent, ether 91 was formed.

We now have a compound which meets the requirements of a precursor of (±)-6. In Wilson's route the double bond of acetate 96 was cleaved using a Lemieux-von Rudloff oxidation.[135] In our initial studies, silyl ether 99 was hydrolysed to the corresponding alcohol 100 with acidic methanol. The reaction was complete within a few minutes and was quantitative. Alcohol 100 was then acetylated with acetic anhydride and pyridine to give 96. The conversion of 98 into 96 was nearly quantitative. When compound 96 (derived from the silyl ether) was treated with an aqueous *tert*-butyl alcohol solution of sodium metaperiodate containing a catalytic amount of potassium permanganate, acetoxy dicarboxlyic acid 101 was obtained as a white crystalline solid in 86% yield. An analytically pure sample (mp 110-111°) was obtained after one recrystallization. The high resolution mass spectrum of 101 exhibits a parent ion with an *m/e* of 260.1255, corresponding to the required formula of $C_{12}H_{20}O_6$. The pmr and ir spectra of the product are in complete accord with the proposed structure of 101. There was no melting point depression of a mixture of samples of 101 prepared directly *via* Wilson's route and by the more efficient silyl ether route.



Treatment of 101 with methanolic sodium methoxide effects hydrolysis of the acetate group, and upon acidification to pH 1, a white crystalline lactonic acid was isolated in quantitative yield after chromatography on silicic acid.

Subsequently we found that silyl ether 99 could be subjected directly to the Lemieux-von Rudloff oxidation. Upon acidification during the workup, the silyl ether was hydrolysed off and a lactonic acid, identical to that obtained *via* the two step process outlined above, was obtained in 87% yield.

An analytically pure sample (polymorphic; mp 112-113°, 119-120°) of the lactonic acid was obtained after one recrystallization. The pmr and ir spectra of this lactonic acid are identical in all respects to those of the natural Djerassi-Prelog lactonic acid (+)-6. [Samples of (+)-6 were kindly provided by Professors V. Prelog and C. Djerassi.] In addition, the corresponding methyl esters 25, prepared from the synthetic and natural lactonic acids using diazomethane, exhibit identical pmr and ir spectra. Since the lactone ring imposes conformational constraints on the acid and its methyl ester, the various possible diastereoisomers should display very different patterns in their pmr spectra for the three methyl doublets. This difference was evident in the pmr spectra of the diastereoisomers 24, prepared by Bergel'son and Batrakov[94] (see Chapter 2), although of course none of these compounds has the same spectra as our material. The six methyl lines in the pmr spectra of the natural and synthetic acids and methyl esters were calibrated. Agreement in chemical shift values between the natural and synthetic pairs was excellent, as can be seen in Table 6 which gives the data for the methyl esters.

The results of a pmr and cmr study of (±)-6 are given in Tables 7 and 8, respectively.

On the basis of the evidence given in this chapter, we are confident that our synthetic lactonic acid is the racemic form of the Djerassi-Prelog degradation product.

The synthesis of (±)-**6** from the intermediate lactone **86** has been achieved in an overall yield of 65% tripling the previous yield obtained by Wilson. In addition, an efficient synthesis of diacid **68** has been achieved.

Table 6: Chemical Shifts of the Methyl Signals in (±)-**25** and (+)-**25**

Methyl Signal	Chemical Shift (Hz) from TMS	
	(±)-**25**	(+)-**25**
1	125.6	125.9
2	119.9	119.8
3	119.6	118.9
4	113.4	112.9
5	102.4	102.3
6	96.3	96.0

Table 7: Pmr Analysis of (+)-6

Proton Irrad'd	Chemical Shift (τ) and Multiplicity[a] (Hz)									
	COOH	H_3	H_2	H_6	H_{5A}	H_4	H_{5B}	C_6-CH_3	C_2-CH_3	C_4-CH_3
	1.3	5.42	7.26	7.51	ca. 8.0	ca. 8.1	ca. 8.55	8.72	8.81	8.99
	bs	d,2.4	q,7.1		m	m	m	d,6.9	d,7.2	d,6.9
		d,10	d,2.4							
H_3			q,7.1	--	--	**	--			
H_4		**					**	--	--	bs
H_2		d,10			--		*[b]	--	s	--
H_6		--			**		**	bs	--	--
H_{5A}							**			

a) For an explanation of the multiplicity abbreviations see page 142.

b) Likely the H_2-decoupling frequency was overlapping a portion of the H_6 signal. A small effect of H_{5B} is observed.

* Signal appearance slightly altered.

** Signal appearance strongly altered.

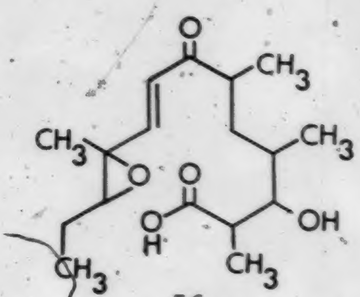
Table 8: Cmr Analysis of (±)-6

Signal	Chemical Shift (ppm from TMS)	ORD Multiplicity	Assignment
1	8.42	doublet	C_6
2	16.94	quartet	C_6-methyl
3	17.21	quartet	C_4-methyl
4	30.97	quartet	C_2-methyl
5	36.31	doublet	C_4
6	37.28	triplet	C_5
7	41.16	doublet	C_2
8	86.42	doublet	C_3
9	174.63	singlet	C_7
10	177.75	singlet	C_I

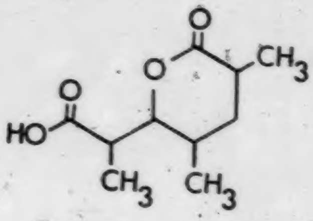
CHAPTER 6

THE LEFT HAND SIDE OF METHYNOLIDE

Since the double bond of the α,β-unsaturated carbonyl of compound 56, a potential precursor of methynolide, has the E configuration, the reaction of a suitable aldehyde with a stabilized phosphorane derived from the lactonic acid (±)-6, which constitutes the right hand portion of 56, should yield a compound with the desired geometry.[136] The stereochemistry of the required aldehyde[91b] is such that 2-methyl-2-pentenal 102, the aldol self-condensation product of propanal, or its epoxide* 103 can be used in the synthesis.



56



(±)-6

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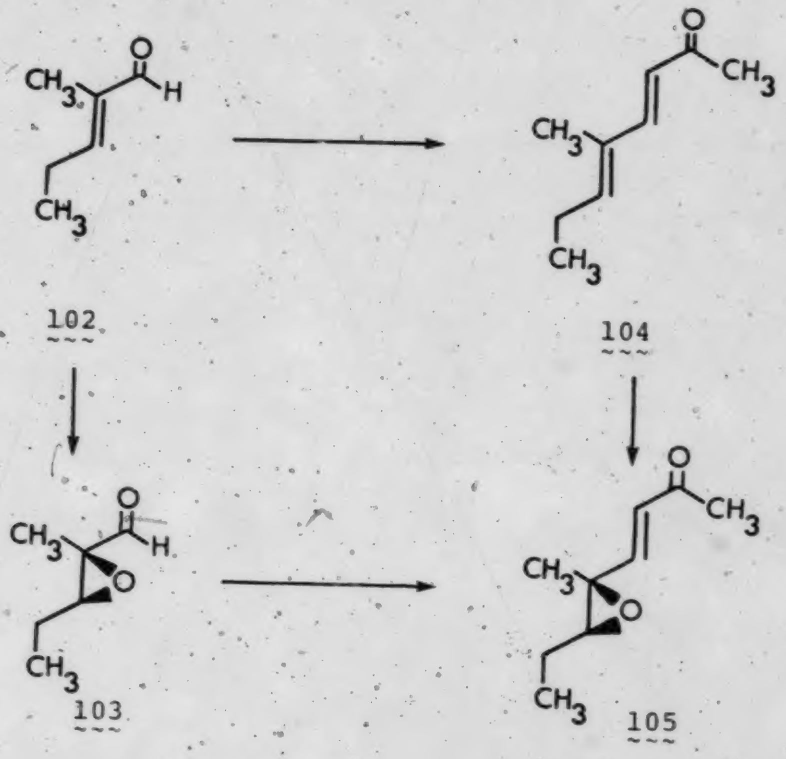
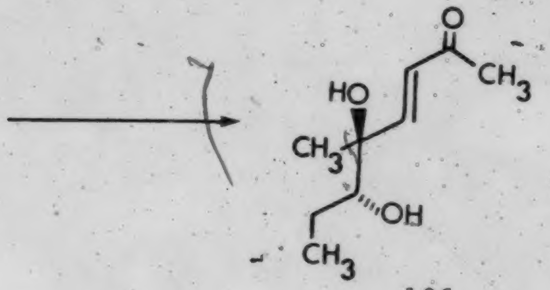
[*] Prepared via reduction of 102 to the corresponding alcohol, epoxidation, and reoxidation to aldehyde 103.

The stereochemistry of the double bond of 102 was conclusively established recently[137] although 102 has been known for many years.



G. Spessard carried out model studies to test this scheme and found that the Wittig reaction did indeed proceed in the expected manner. Condensation of 102 with triphenyl(acetylmethylene) phosphorane[138] provided the product 104 in good yield, and subsequent treatment of 104 with 3-chloroperbenzoic acid resulted in oxidation exclusively at the γ,δ double bond to produce 105. This epoxide behaved in a normal manner, since the γ position of the α,β-unsaturated ketone is less prone to develop a positive charge in the ring opening of the epoxide despite its being more highly substituted, and was converted into diol 106 by two phase treatment with aqueous sulphuric acid in tetrahydrofuran. Compound 106 thus contains all of the stereochemical features present in the C_7-C_{13} fragment of methynolide.

105

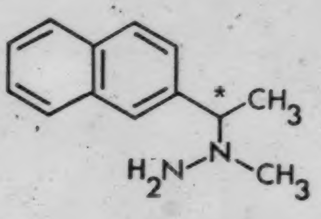


106

Epoxide 105 could also be obtained from epoxy aldehyde 103 directly. With 103 the Wittig reaction proceeds faster and in slightly higher yield than in the case of 102. Since the acyl group employed in the actual synthesis of methynolide is expensive, and as one less step is required in the reaction sequence, the use of epoxy aldehyde 103 is to be preferred.

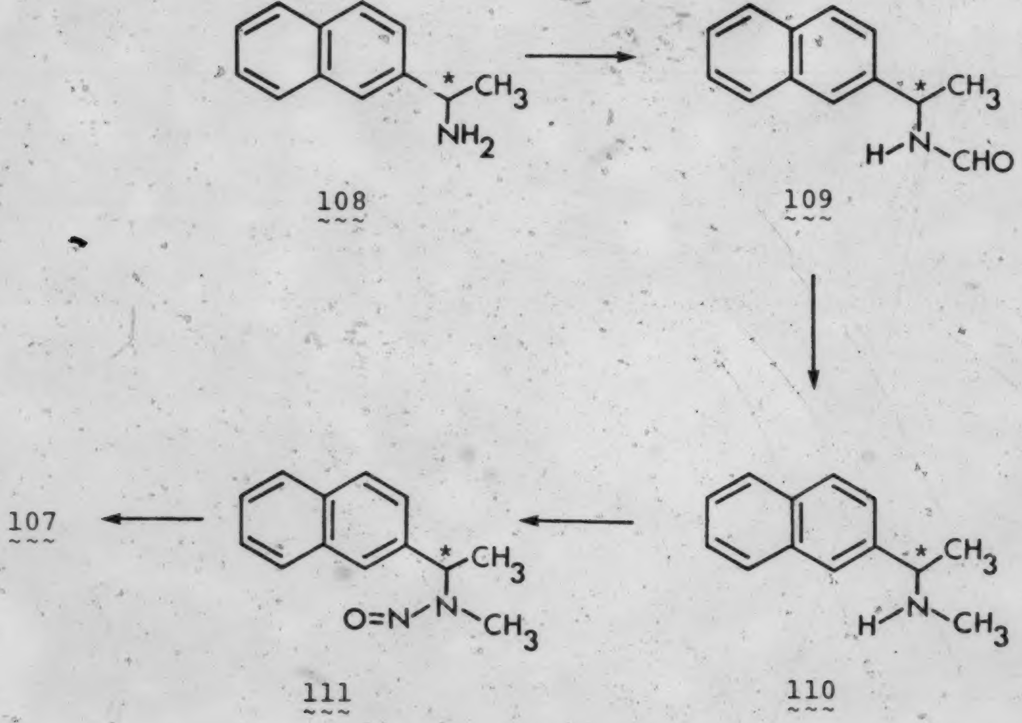
As was outlined previously in Chapter 4, the overall synthetic route involves the use of an optically active left hand portion to resolve the right hand side of the aglycone during the cyclization process. Rickards *et al.*[91b] had established the absolute stereochemistry of the left hand portion of methynolide, and thus 103 with the absolute configuration indicated (which turned out to be the (+)-enantiomer) was required for the Wittig reaction. The use of aldehyde (±)-103 in the reaction instead of pentenal 102 has a further advantage as noted above.

Since (±)-103 was readily available, we first decided to resolve this aldehyde by utilizing an optically active carbonyl reagent. This work was carried out by H. Ona. He chose hydrazine derivative 107 as the resolving agent for two reasons: (1) many optically active amines have become available, very often in both the (+) and (-) forms and (2) hydrolysis of hydrazones after resolution appears to proceed satisfactorily.[139]



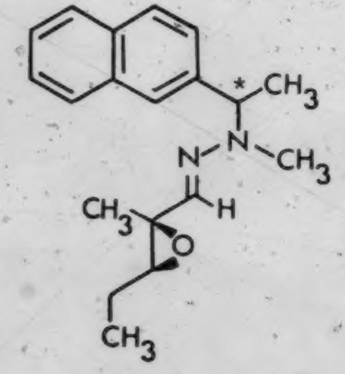
107

Compound 107 was successfully prepared starting with α-(1-naphthyl)ethylamine 108,[140] according to the scheme shown on the next page. Hydrazine 107 was found to react with common aldehydes and ketones such as heptanal, benzaldehyde, acetone, and cyclohexanone giving stable hydrazones. However, with 103, the hydrazone product 112 was extremely sensitive toward acid, and chromatographic separation of the diastereoisomers was only partially successful on a small scale (50-100 mg).



108 109 110 111 107

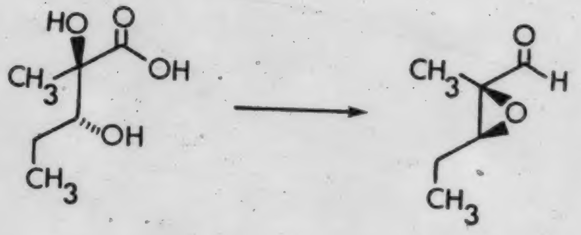
We concluded at this stage that the above method appeared impractical for the resolution of 103, and we decided to resort to a conventional, and accordingly more secure,



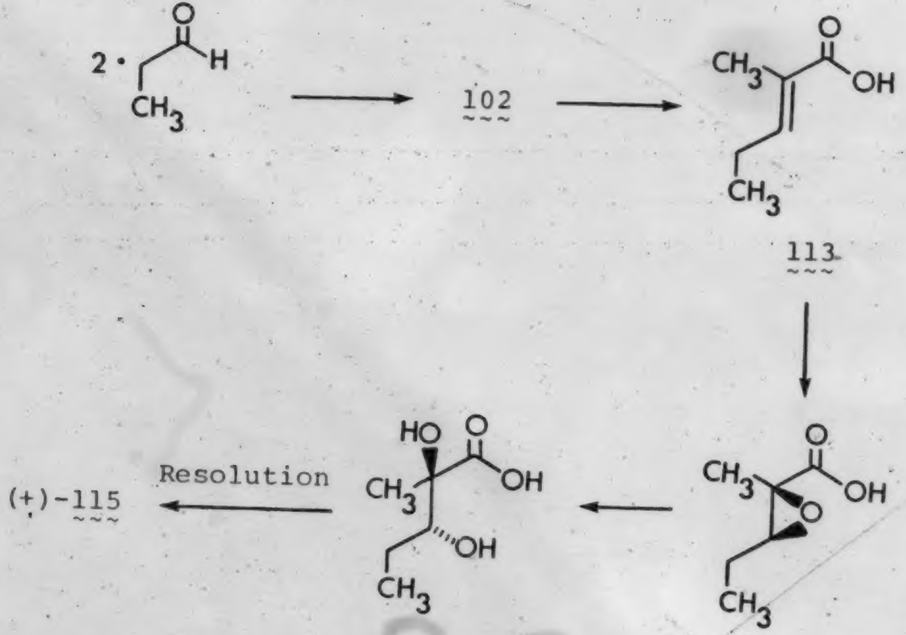
112

route to obtain the desired enantiomer of 103.

The optically active aldehyde (+)-103 was obtained from the (+)-dihydroxy acid 115 prepared according to the method reported by Bergel'son.[141] Propanal was subjected to an aldol condensation[142] to give 102, which was then oxidized with silver oxide to the corresponding carboxylic acid 113. This acid was then epoxidized



(+)-115 (+)-103

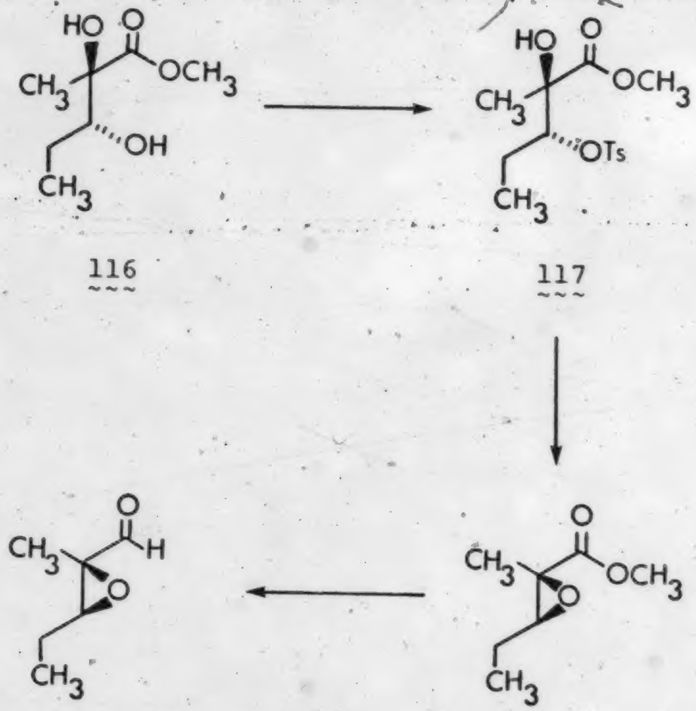


102 113 114 (±)-115 (+)-115

using hydrogen peroxide and acetic acid to give 114 which was immediately treated with aqueous sodium hydroxide to give the racemic diol carboxylic acid 115.

Resolution of (±)-115 was accomplished with the aid of L-(+)-*threo*-2-amino-1-(4-nitrophenyl)-1,3-propane diol. After hydrolysis of the [(+)base·(+)acid] salt, crystalline (+)-2*R*,3*R*-dihydroxy-2*R*-methylpentanoic acid, melting point 149-151°, was obtained in 98% yield. The resolved acid had $[\alpha]_D^{25}$ + 13.1° (*c* 3.02, H_2O) which indicated an optical purity of at least 95% based on the original literature (*vide infra*).[141]

Acid (+)-115 then was converted into its methyl ester 116 using diazomethane. The (−)-enantiomer of this ester could not be detected in the pmr spectrum (see experimental). Ester 116 was then converted into



116

117

118

(+)-103

monotosylate 117 in 83% yield, and subsequent treatment with triethylamine effected cyclization to compound 118. Careful reduction of ester 118 with diisobutylaluminum hydride[143] produced the desired optically active epoxy aldehyde (+)-103.

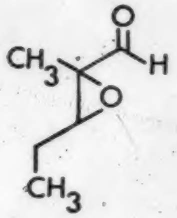
CHAPTER 7

COMPLETION OF THE SYNTHESIS OF METHYMYCIN

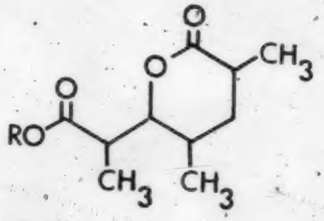
This chapter is included at the request of Professor Masamune in order that a complete report of the total synthesis of methymycin is available in a single thesis. The experiments in this chapter were carried out by H. Yamamoto and A. Fukuzawa, who worked on the aglycone synthesis and the attachment of the sugar residue, respectively, and by S. Kamamta and W. Schilling who contributed to the development of the mercury(II) reagent used in the cyclization of methynolide.

A) SYNTHESIS OF METHYNOLIDE

We now have available the resolved left hand portion (+)-**103** and the racemic right hand portion (±)-**6** of the aglycone precursor **56**. All of the required stereochemistry

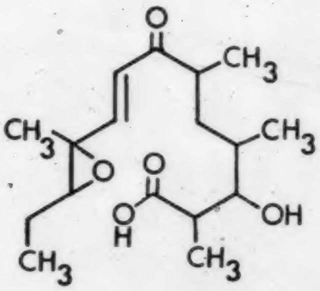


103



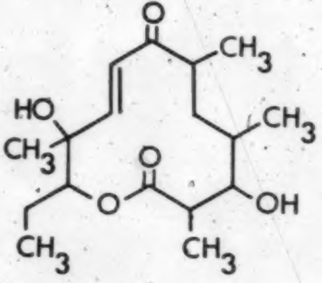
6 R = H

25 R = CH_3



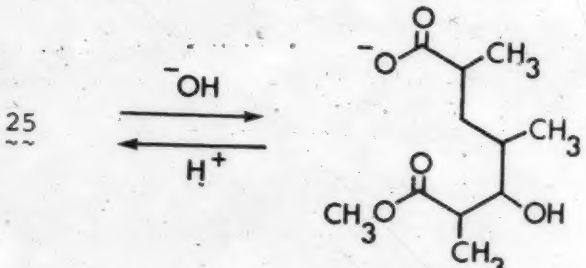
56

of methynolide 14 has been introduced into the former two fragments. The problem thus remained to join 103 and 6 together, followed by opening of the epoxide with subsequent lactonization to give methynolide.



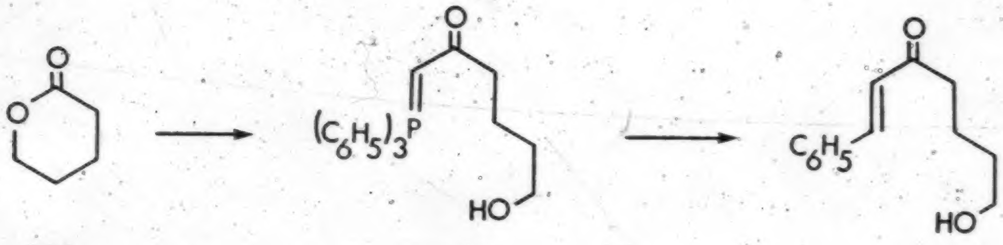
14

We began our investigation with a study of methyl ester 25. The δ-lactone ring of this compound is very stable and recloses rapidly upon acidification of the hydrolysed form 119 of the methyl ester. It



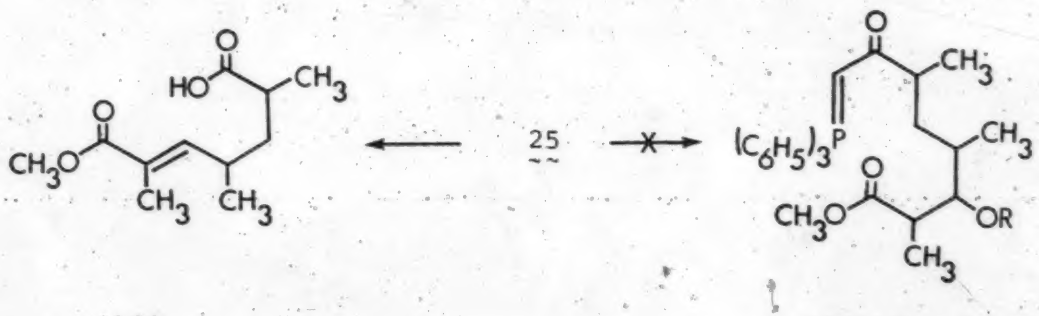
119

was estimated that the lactone of 25 is opened by hydroxide at least 1000 times faster than the methyl ester is hydrolysed. We hoped to make use of this high reactivity by employing a stabilized phosphorane[145] to open the lactone. Model studies carried out with 5-hydroxypentanoic 1,5-lactone 120 were very successful. Reaction of 120 with triphenylmethylene phosphorane



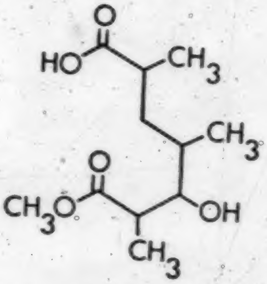
120 121 122

gave the new ylid 121 and subsequent treatment with benzaldehyde provided compound 122 in 30% yield. However, when the same reaction was attempted on 25, elimination occurred to form 123 due to the basic nature of the phosphorane.[146] Thus we were forced to try



123 124 R = H

indirect routes in order to obtain 124. The potassium salt of 119 could be obtained in quantitative yield by treating 25 with potassium hydroxide in aqueous tert-butyl alcohol. Because of the ease of lactone formation, which proceeds even at pH 7, the free carboxylic acid 125 could not be isolated. Treatment of 119



125

with phenacyl bromide in an attempt to trap the carboxylic acid led to recovery of lactone 25. Therefore, we resorted to another more efficient method to trap either the hydroxy or the carboxy group of 119 before ring closure could occur. A reagent which met these requirements was tert-butyldimethylsilylimidazole.[147] Reaction of 119 with four equivalents of the imidazole in N,N-dimethylformamide produced disilyated compound 126. Careful partial hydrolysis[*] of 126 with 0.95 equivalents of potassium hydroxide gave siloxy carboxylic acid 127 in 90% yield from lactone 25. The carboxy function was clearly evident from the presence of the broad hydroxy absorption from 3400 to 2300 cm^{-1} in the ir spectrum, accompanied by a carbonyl peak at 1705 cm^{-1}. The silyl ester peaks at τ 9.12 (9H) and τ 9.75 (6H) which were present in the pmr spectrum of **126** were absent from the spectrum of **127**, further confirming formation of the carboxylic acid. Since **127** was relatively sensitive towards acid (hydrolysis and lactonization back to **25**) and base (elimination to produce **123**), transformation of **127** into the corresponding acylmethylene phosphorane required careful selection of reaction conditions. Conversion of **127** into imidazolide **128** with N,N-carbonyldiimidazole,[148] followed by treatment with one equivalent

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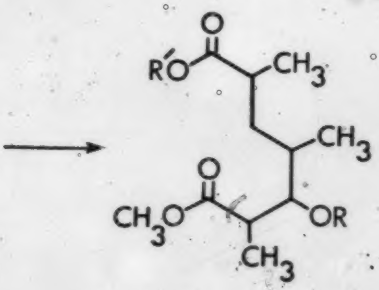
[*] Corey[147] reports that silyl esters are hydrolysed approximately twenty times faster than silyl ethers.

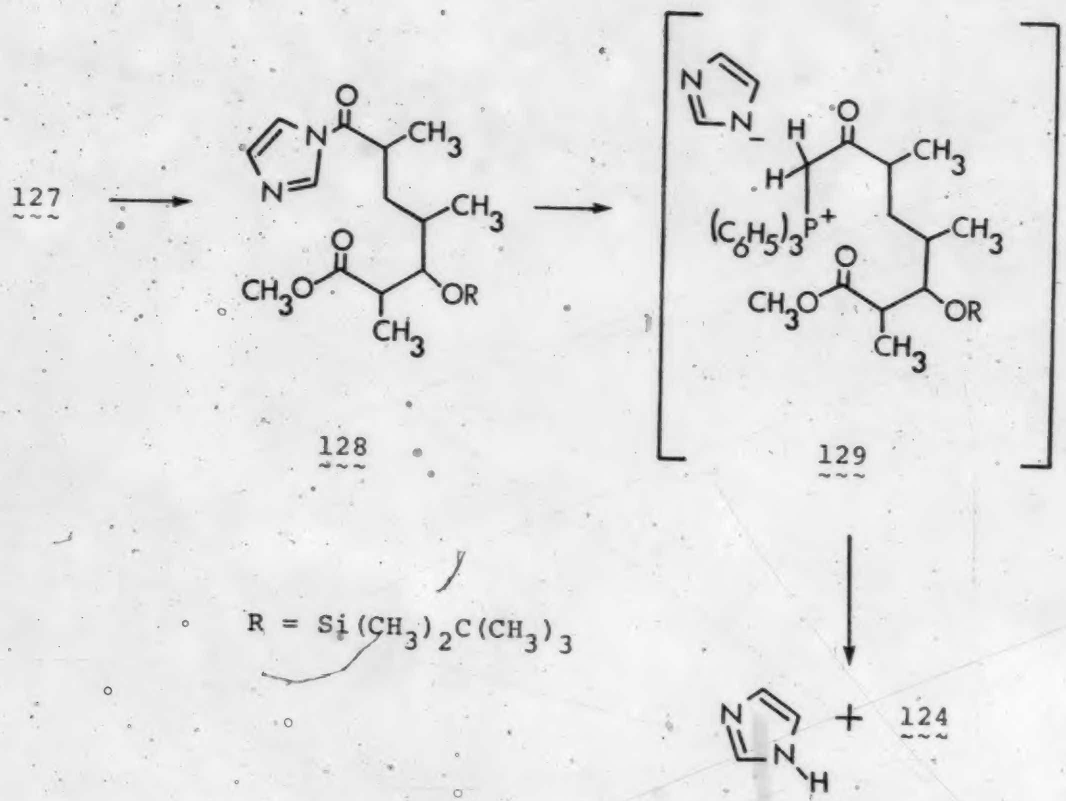
119



126 R' = R = $Si(CH_3)_2C(CH_3)_3$

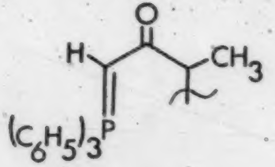
127 R' = H R = $Si(CH_3)_2C(CH_3)_3$

of salt-free triphenylmethylene phosphorane[145] in benzene led to the desired Wittig product **124** in 95% yield. All signals in the pmr spectrum of **124** were assignable. The vinyl absorption appearing as a broad doublet at τ 6.3 in the pmr spectrum along with the 1535 cm^{-1} absorption in the ir spectrum confirmed the formation of the

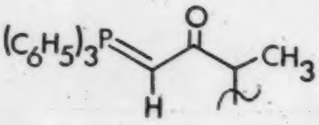


$R = Si(CH_3)_2C(CH_3)_3$

phosphorane. An interesting feature of the pmr spectrum was the presence of two methoxy signals at τ 6.47 and 6.53 in the approximate ratio of 1:1. We believe that these two signals are present since the product is a mixture of both the s-*trans* and s-*cis* isomers of 124.



s-trans



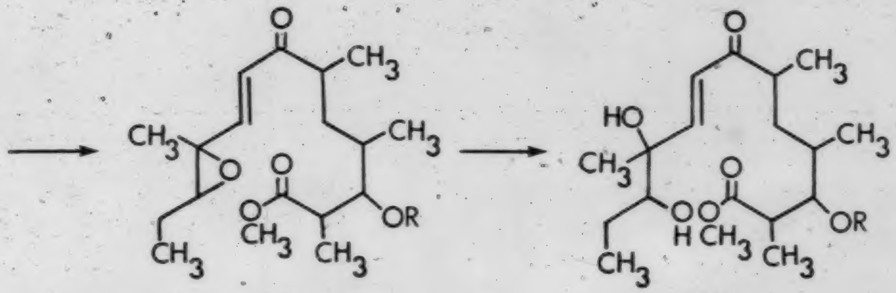
s-cis

The introduction of the phosphorane proceeds under essentially neutral conditions. The ylid initially attacks the imidazolide to produce salt **129**. Since the pKa's of acylphosphoranes normally range between 4.5 and 10,[136] the imidazole anion (pKa 15) was able to instantly abstract the acidic methylene proton to form imidazole and the new phosphorane **124**. The use of two equivalents of triphenylmethylene phosphorane as recommended in the literature[145a] must be avoided, since elimination to **123** or its equivalent occurs readily.

Reaction of **124** with aldehyde (+)-**103** in refluxing toluene for two days effected condensation to produce a diastereomeric mixture (presumably 1:1) of **130** in 60% yield. Despite the fact that the product is obviously a mixture, the pmr of the product was extremely clean indicating that the magnetic influence of one portion, the right hand side for instance, on the other is only slight, as might be expected. Again all pmr signals were assignable. The newly introduced double bond clearly had the *E* configuration since there were a pair of doublets in the pmr spectrum at τ 3.32 and 3.64 with a 16 Hz coupling, which is typical of *trans*-coupled vinyl protons.[87] The double bond was further confirmed by the ir absorption at 1625 cm^{-1}

and by a 1690 cm^{-1} peak indicative of an α,β-unsaturated ketone. Treatment of 130 with aqueous sulphuric acid in tetrahydrofuran effected opening of the epoxide to give 131, a potential methynolide precursor. This diastereomeric mixture again showed discernible ir and pmr signals attributable to all of the functionalities present in 131.

124



130

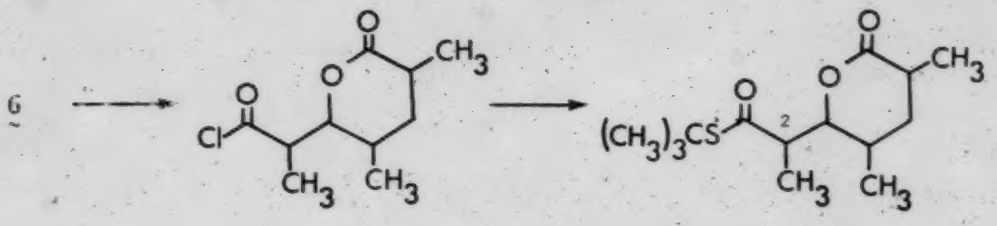
131

R = $Si(CH_3)_2C(CH_3)_3$

Unfortunately, all attempts to hydrolyse seco-ester 131 to the corresponding seco-acid met with failure. Total destruction of the skeleton *via* reverse aldol and elimination reactions occurred. Compound 131 was thus a dead-end compound without the aid of a suitable enzyme (*e.g.* carboxy esterase) to hydrolyse the methyl ester.

The successful formation of seco-ester 131 was however, very encouraging. It was only necessary to substitute an appropriate protective group for the methyl ester portion of 131. The protecting ester must exhibit reasonable stability towards both acid and base, and must also be removed with great ease. It would also be desirable if the removal of this protecting group could be accompanied by lactone formation. The *S*-*tert*-butyl thioate group was selected for use in the modified route to methynolide.

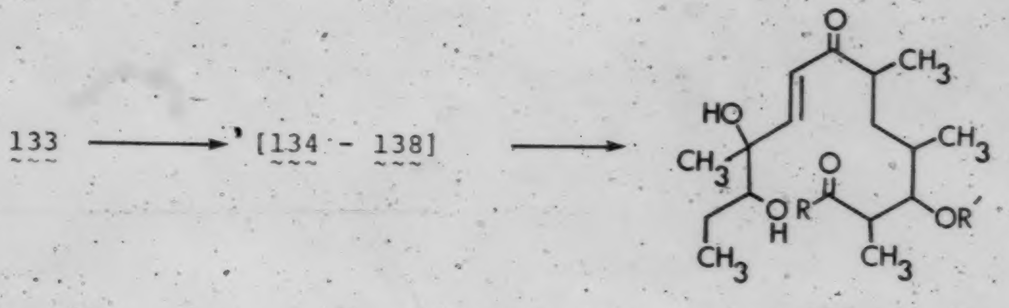
When acid chloride 132, obtained from 6 by treatment with oxalyl chloride in benzene, was reacted with 2-methylpropane-2-thiol, the C_2 position of thiol ester 133 was epimerized, presumably by the hydrogen chloride evolved in the condensation reaction. Standard Schötten-Baumann conditions gave only about a 50% yield of 133. It was therefore necessary to find a more efficient and milder method of making this thiol ester. As this entire project developed, it became increasingly clear that there was a need to invent a general, selective procedure for the preparation of thiol esters. A great deal of effort has been expended towards this goal, and



132

133

the satisfactory outcome is discussed in detail in Part II of this thesis. In the case of the conversion of 6 into 133, the problem turned out to be simple because of the availability of acid chloride 132. Thus, the reaction of 132 with thallium(I) 2-methylpropane-2-thiolate was found to proceed quantitatively, with no epimerization, to give 133. This thiol ester was then reacted further following the methods described above for the conversion of 25 into 131, to give seco-thiol ester 139.



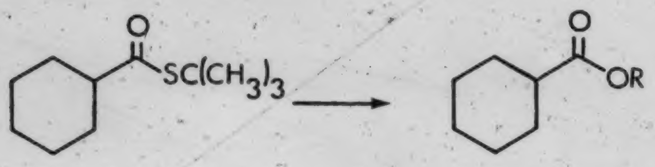
139

$R = SC(CH_3)_3$

$R' = Si(CH_3)_2C(CH_3)_3$

The thiol ester function survived all the operations as indicated by the pmr and ir spectra of each intermediate (134 - 138) and 139. These spectra match very well with those of the corresponding methyl ester compounds, except of course for the absorptions due to the different ester functions, and are described in Chapter 8 which deals with the experimental procedures. The s-trans and s-cis mixture was again discernible in the pmr spectrum of the phosphorane, and the E configuration of the double bond introduced via the phosphorane was evident from the large coupling between the vinyl protons. The thiol ester has a typical ir absorption band at approximately 1675 cm^{-1} and there is a sharp singlet in the pmr spectrum at about τ 8.55 due to the tert-butyl protons of the thiol ester.

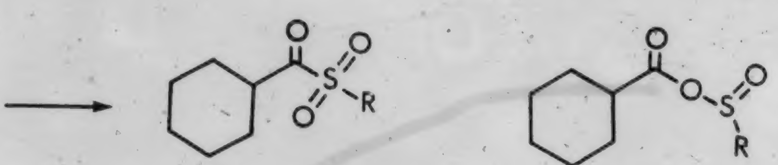
We first investigated methods for the activation of thiol esters in preparation for cyclizing 139 to methynolide. Model studies for the oxidative activation[149] of 140 in order to effect direct conversion into its esters and acid were encouraging. The addition of three equivalents of 3-chloroperbenzoic acid to a 1:3 mixture of 140 and an alcohol in dichloromethane at -70° and subsequent warming to room temperature, over two hours, provided the corresponding esters 141 in yields ranging from 75 to 95%. Alcohols used were methanol, cyclohexanol, cyclohexylmethanol, 2,4-dimethylpentan-3-ol,



140 141

and 4-methyloct-5-ene-7-one-3,4-diol. Under the above conditions 140 was oxidized to the α-carbonyl sulphone 142 or to the corresponding sulphite ester 143

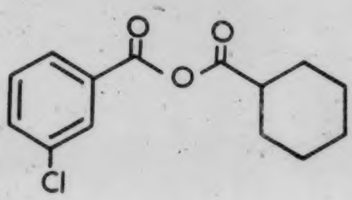
140



142 143

R = $SC(CH_3)_3$

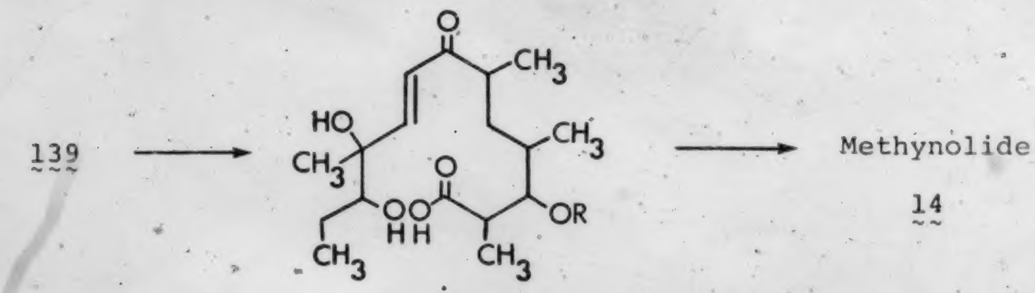
of cyclohexanecarboxylic acid. These intermediates were readily attacked by either the alcohol or the 3-chlorobenzoic acid present to provide compounds 141 and 144, respectively, at the initial stage of the reaction. The latter compound reacted further with the



144

hydroxy compound upon prolonged heating, and high yields of 141 were eventually attained. In the absence of external nucleophiles such as alcohols however, 142 and/or 143 appear to undergo a complicated series of reactions including disproportionation and further oxidation.[149] In order to obtain the free carboxylic acid, the reaction was carried out in aqueous tetrahydrofuran.

However, when attempts were made to lactonize **139** directly using the oxidative activation method, extensive formation of what appeared to be a mixture of the anhydride of **145** and the mixed anhydride of **145** and 3-chlorobenzoic acid took place. The mixed anhydride with 3-chlorobenzoic acid was clearly too weak to effect lactonization and more powerful activation was required. Thus seco-acid **145**, obtained by oxidative hydrolysis of **139** in wet tetrahydrofuran, was treated with 1.2 equivalents of trifluoroacetic acid anhydride in benzene. The selection of conditions was difficult,



139 → **145** → Methynolide **14**

145

R = $Si(CH_3)_2C(CH_3)_3$

but eventually the above procedure led to what appears to be a maximum yield attainable by this method. These conditions were sufficient to hydrolyse the silyl ether as well as to effect lactonization to methynolide. After recrystallization from ether-hexane, the synthetic methynolide was obtained in up to 25% yield. This yield is based on the amount of the desired diastereoisomer, estimated to be 50%, present in **139**. The fate of the other isomer has not been defined but appears to be uncyclized under the conditions employed for the lactonization. The identity of the synthetic material was evident by spectral comparison, including CD which indicated 95% optical purity of natural methynolide.

Because of the fluctuation in the yield and difficulties encountered in optimizing the lactonization conditions, a more reliable and direct lactonization of **139** to **14** was sought.

The electrophilicity of mercury(II),[150] in particular towards bivalent sulphur (soft-soft combination), is well known.[151] Examples include the oxidative cleavage of dithianes. However, it is rather surprising that reactions of mercury(II) and isoelectronic thallium(III)[152] with thioates have received virtually no attention in the past except for presumably only two reports which appeared in the 1920's. Sachs describes that mercury(II) cleaves *S*-ethyl ethanethioate, with extreme ease, to form sulphur-containing mercuric salts.[153] It was hoped that this affinity of mercury(II) could be extended to the formation of esters and lactones from the corresponding *S*-*tert*-butyl thioates. Model studies were again carried out using **140**. Ester formation was studied with respect to reagent, solvent and the alcohols to be condensed. The results are summarized in Table 9. For secondary, tertiary, and hindered primary alcohols, the reaction proceeds very efficiently at room temperature when mercury(II) trifluoroacetate in acetonitrile is used. More recently, the corresponding mesylate has been used with even greater success. The combination of mercury(II) chloride and cadmium carbonate is the preferred choice for the formation of methyl and ethyl esters. Mercury(II) acetate and thallium(III) salts were found to be inefficient at bringing about esterification.

The reaction mechanism for the esterification is not entirely clear. It was found that in the absence of alcohols, a mixture of 140 and mercury(II) trifluoroacetate forms cyclohexanecarboxylic trifluoroacetic anhydride, as confirmed by ir spectroscopy. However, preliminary control experiments appear to indicate that the efficient ester formation with sterically hindered

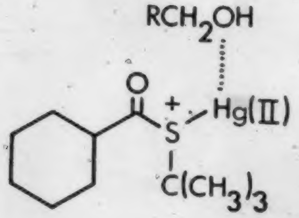


Table 9: Reaction of Hg(II) and Tl(III) with

S-*tert*-Butyl Cyclohexanemethanethioate (140) and Alcohols

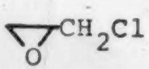
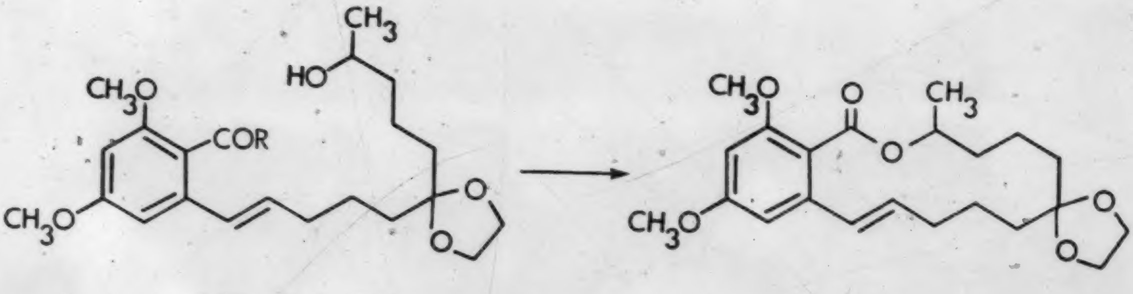
Entry	Alcohol	Reagent	Base	Solvent	Reaction Time	Yield
1	CH_3OH	$HgCl_2$	$CdCO_3$	acetonitrile	reflux, 3 hr	98%
2	C_2H_5OH	$HgCl_2$	$CdCO_3$	acetonitrile	reflux, 3 hr	90%
3	CH_3OH	$Hg(OSO_2CH_3)_2$	----	acetonitrile	r.t., 10 min	65%
4	$C-C_6H_{11}-CH_2OH$	$Hg(OSO_2CH_3)_2$	----	acetonitrile	r.t., 10 min	100%
5	$C-C_6H_{11}-OH$	$HgCl_2$	$CdCO_3$	acetonitrile	reflux, 3 hr	97%
6	$C-C_6H_{11}-OH$	$Hg(OCOCF_3)_2$	----	acetonitrile	r.t., 5 min	96%
7	$C-C_6H_{11}-OH$	$Hg(OSO_2CH_3)_2$	----	acetonitrile	r.t., 10 min	100%
8	$C-C_6H_{11}-OH$	$Hg(OCOCH_3)_2$	$CdCO_3$	acetonitrile	reflux, 15 hr	41%
9	$C-C_6H_{11}-OH$	$Tl(OCOCF_3)_3$	----	acetonitrile	r.t., 5 min	55%
10	$(CH_3)_3COH$	$Hg(OCOCF_3)_2$	----	acetonitrile	r.t., 5 min	100%
11	$(CH_3)_3COH$	$Hg(OCOCF_3)_2$	----	dichloromethane	r.t., 5 hr	82%
12	$(CH_3)_3COH$	$Hg(OSO_2CH_3)_2$	Na_2HPO_4	acetonitrile	r.t., 1 hr	100%
13	$(CH_3)_3COH$	$Hg(OSO_2CH_3)_2$		acetonitrile	r.t., 1 hr	91%

Table 9: Continued

Entry	Alcohol	Reagent	Base	Solvent	Reaction Time	Yield
14	$(CH_3)_3COH/(CH_3)_3C\overset{\overset{O}{\|}}{C}S(CH_3)_3$	$Hg(OSO_2CH_3)_2$	Na_2HPO_4	acetonitrile	r.t., 6 hr	93%
15	$(CH_3)_3COH$	$Hg(OCOCH_3)_2$	$CdCO_3$	acetonitrile	reflux, 15 hr	22%
16	CH_3OH	$Tl(OCOCF_3)_3$	----	acetonitrile	r.t., 5 min	44%

alcohols proceeds mainly through co-ordination of the alcohol with the mercury(II), followed by collapse into the ester and mercuric salts. The mixed anhydride is converted approximately ten times more slowly into the oxy-ester, under the specified conditions, than when the reaction is carried out in the presence of mercury(II). This indicates that at most 10% of the product is derived *via* the mixed anhydride. The extent to which this co-ordination process competes with the conventional mixed anhydride pathway also seems to depend largely on the structures of the alcohols used.

In order to test the extension of this esterification method to the formation of lactones, (±)-O,O-dimethylzearalenone seco-acid ethylene ketal 146[105] was used as a substrate. Thiol ester 147, dissolved in acetonitrile at room temperature, cyclized immediately upon addition of two equivalents of mercury(II) trifluoroacetate to give a near quantitative yield of lactone 148.



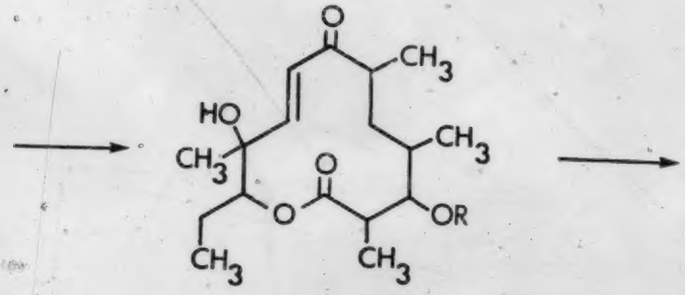
146 R = OH

147 R = $SC(CH_3)_3$

148

This new method of lactonization was then tried on 139. Use of two equivalents of mercury(II) trifluoroacetate, to activate the thiol function of 139, in acetonitrile effected lactonization to the silylated methynolide 149 in one hour. This material was identical in all respects to 149 prepared from natural methynolide. The silyl ether was then hydrolysed with a tetrahydrofuran solution of tetrabutylammonium fluoride to afford 14 consistantly in 20-30% overall yield from seco-thiol ester 139. In view of the difficulty involved in forming

139



Methynolide

14

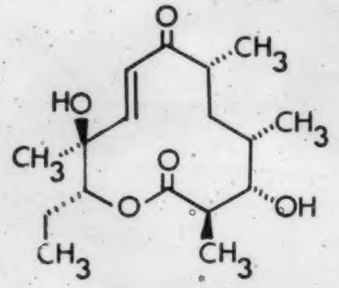
149

R = Si$(CH_3)_2C(CH_3)_3$

a twelve-membered lactone ring, in particular in the case of methynolide, due to the expected van der Waals interaction of the three inner hydrogen atoms discussed in Chapter 4, this yield must be deemed to be a great success. In this way our initial objective, a test of our prediction based on the conformational analysis, has finally been achieved.

B) CONVERSION OF METHYNOLIDE INTO METHYMYCIN

In order to complete the synthesis of methymycin 12, the only remaining task was to effect glycosylation[154] of methynolide 14 with desosamine 150.



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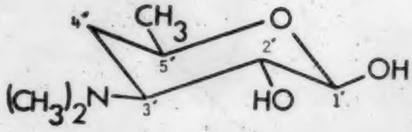

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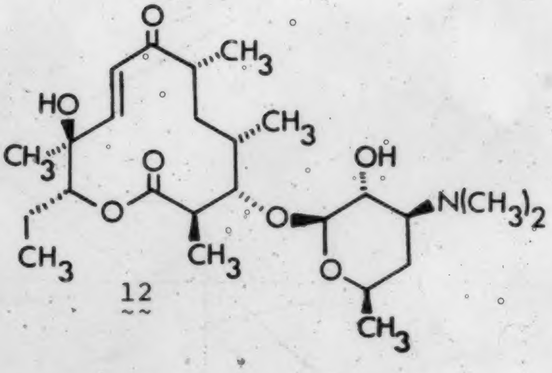
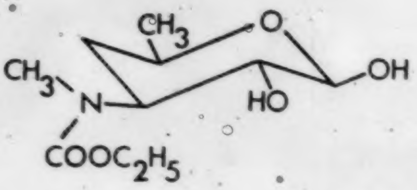


12

Glycosylation of tert-amino sugars has never been achieved previously, and it was anticipated at the outset that this would present some problems in completing the present task. There are two functional groups attached to desosamine at sites other than the anomeric centre. The hydroxy group at the $C_{2'}$ position can be protected during the process of glycosylation by acetylation, since it is known that the resulting 2'-acetoxymethymycin can be hydrolysed to methymycin.

The second problem involves the dimethylamino group at the $C_{3'}$ position. It was expected and indeed was very evident in early experiments that if this group becomes free (deprotonated) during the glycosylation, then the basic nitrogen immediately participates in the reaction at the anomeric centre, resulting in a complex, very often intractable, mixture of products.

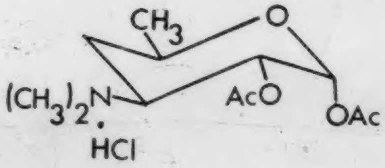
In order to circumvent this unfavourable situation, several attempts were made, including the use of compound 151 derived from desosamine, to protect the amino group.



151

These results are elaborated upon in A. Fukuzawa's research report (March 1975) and are not included in this thesis. Eventually we came to the conclusion that any modification of the amino functionality and subsequent conversion back to the dimethylamino group after the glycosylation, involved processes which normally destroyed the aglycone and/or sugar moities, and that the only practical way to meet the challenge was to devise conditions which would maintain the dimethylamino group as the hydrochloride (or bromide) during the glycosylation. It was found after all that one of the simplest glycosylation procedures,[155] the use of 1-bromosugars served the purpose, and that any other more sophisticated, supposedly more selective, in terms of the α- and β-glycoside linkage, methods presented added complications in the preparation of necessary intermediates.

Desosamine hydrochloride was acetylated using acetic anhydride in pyridine to give a mixture of the 1-α and 1-β acetates 152 and 153, respectively.[6,156] The 1-β acetate could be readily separated by fractional crystallization from its 1-α anomer using a chloroform-ethyl acetate solvent system. Pure 153 was obtained as a white solid (mp 194-195.5° decomp) in 78% yield.



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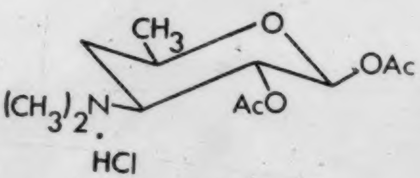
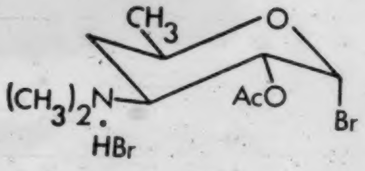


153

A typical axial-axial coupling constant between vicinal protons on a cyclohexane ring is in the range of 5-10 Hz, and the corresponding axial-equatorial coupling is 2-3 Hz. With this information it is a simple matter to identify the α- and β-acetates. There was a 7 Hz coupling between H_1 and H_2 of acetate 153, which is in the expected range for an axial-axial coupling. The corresponding coupling in the β-anomer 152 was 3.5 Hz. In both anomers, the coupling between H_2 and H_3 was 10 Hz as anticipated.

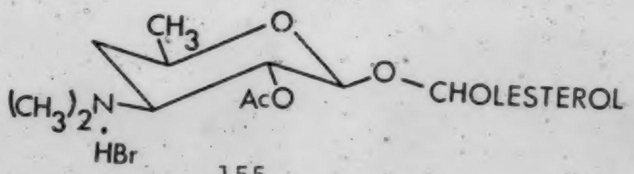
Treatment of 153 with hydrogen bromide in a mixture of acetic acid and acetic anhydride gave a quantitative yield of the unstable 1-α-bromo-2-acetoxy hydrobromide 154.[155] The anomeric assignment was again based on the coupling between the protons on C_1 and C_2 in the pmr spectrum of 154. There was a 4 Hz coupling between these protons, and thus 154 is the α-anomer. This sugar was a crystalline but rather unstable solid



154

(mp 159-168° decomp) and the crude product was employed without further purification for the next step.

With bromide 154 in hand, model studies were carried out in order to find optimal conditions for the glycosylation. When one equivalent of **154** was reacted with cholesterol using lutidine[155] as a solvent, a 40% yield of the β-glycoside hydrobromide **155** was obtained (mp 252-254°) after chromatography. When three equivalents of **154** were used, the yield of **155** increased to 72%. The fact that only the β-glycoside was produced was deduced from the characteristic axial-axial coupling of H_1 and H_2 in the pmr spectrum of the purified material. The choice of lutidine as solvent is clear, since any

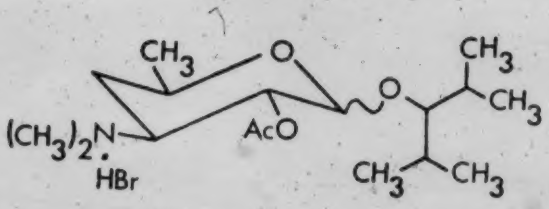


155

base stronger than lutidine, or the use of silver or mercury salts to try and increase the yield, resulted in complete destruction of the sugar moiety, as discussed earlier.

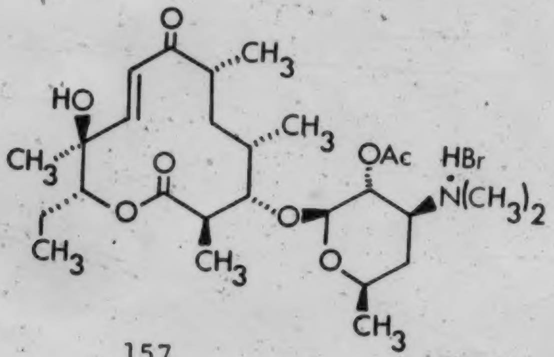
Use of 2,4-dimethylpentan-3-ol, an alcohol more hindered than cholestrol, as the substrate provided a 67% yield of a mixture of α- and β-glycosides **156**.

The synthetic pathway to obtain methymycin called for reaction of methynolide with **154** to give 2'-acetoxy-methymycin hydrobromide **157**, with subsequent hydrolysis


CH3
O
CH3
CH3
(CH3)2N
HBr
AcO
CH3
CH3

156

to produce methymycin. Before proceeding with the glycosylation of the synthetic methynolide, 157 was prepared from naturally occurring methymycin in order to have an authentic sample of 157 for comparison. Acetylation of methymycin was carried out under


O
CH3
HO
CH3
CH3
O
OAc
HBr
N(CH3)2
O
O
O
CH3
CH3
CH3

157

standard conditions and resulted in a mixture of 2'-acetoxymethymycin and 2',10-diacetoxymethymycin[92a] which was separated by preparative thin layer chromatography (ptlc). Treatment of the monoacetoxymethymycin with a chloroform solution of hydrogen bromide gave a quantitative yield of 157.

The synthetic methynolide was then treated with three equivalents of freshly prepared **154** in anhydrous lutidine for 18 hours at 50°. The product was isolated by ptlc, and the ir spectrum of the material was found to be almost superimposable upon that of authentic **157**. The only observable difference was a small peak at 1012 cm^{-1} due to the presence of the α-glycoside in the product. No attempt was made to separate the anomers at this stage.

The mixture of α- and β-2'-acetoxymethymycin hydrobromides was then hydrolysed in a mixture of methanol and triethylamine to provide a readily separable 1:5 mixture of the α- and β-glycosides. This mixture was purified by ptlc without difficulty. The spectra of the synthetic β-methymycin were identical with those of authentic methymycin.

Drs. D. W. Westlake and L. Bryan of the Department of Microbiology at the University of Alberta kindly determined the antimicrobial activity of the synthetic methymycin (β-glycoside) and its anomer (α-glycoside) against Streptococcus pyrogenes group A, type 5. The synthetic compounds exhibited 100% and approximately 20% activity, respectively.

The total synthesis of the macrolide antibiotic methymycin has now been completed. The majority of the work discussed in this thesis has recently been published.[157]

CHAPTER 8

EXPERIMENTAL

All melting points and boiling points are uncorrected.

The pmr and cmr spectra were measured with Varian Associates A-60 or HA-100 spectrometers and a Bruker HFX-10 spectrometer, respectively. Tetramethylsilane was used as an internal standard unless otherwise stated. All coupling constants are reported in Hz. In reporting pmr spectral data, the following abbreviations are used.

s ; singlet
d ; doublet
t ; triplet
q ; quartet
quin ; quintet
sept ; septet
m ; multiplet
b ; broad
c ; complex (one or more small couplings which overlap the main splitting).

The ir spectra were obtained on a Perkin-Elmer Model 257 infrared spectrometer. All absorption positions are reported in cm^{-1}. In reporting ir spectral absorptions, the following abbreviations are used.

s ; strong

m ; medium

w ; weak

b ; broad

The mass spectra were obtained with A.E.I. MS-2 and MS-9 spectrometers.

The glpc analyses were performed on a Hewlett-Packard model 7620 research chromatograph equipped with 1.8 m x 0.3 cm columns (packing indicated in the text) and a flame ionization detector.

The pH 7 buffer solution was prepared by dissolving potassium dihydrogen phosphate (9.1 g) and disodium hydrogen phosphate (18.9 g) in water and adjusting the total volume to 1 l.

All reactions were carried out under a dry argon atmosphere. A rotary evaporator (water aspirator) was used for the removal of solvents from all reaction mixtures unless otherwise specified.

Bisfumaronitrile Nickel(0)

The reaction was carried out in a fume hood because of the toxicity of the nickel(0) tetracarbonyl. The procedure used was that reported by Schrauzer.[117]

Nickel(0) tetracarbonyl (ca. 5 ml, 38 mM) was added to a solution of fumaronitrile (2.0 g, 25 mM) in anhydrous acetone (30 ml). The orange-red mixture was refluxed (dry-ice condenser) for 6 hr and then the heat source was removed. The reaction mixture was stirred at room temperature for 18 hr in order to allow the excess nickel(0) tetracarbonyl to evaporate. The red-brown pyrophoric complex was collected by filtration through Celite to give 5.4 g (100%) of product which was used directly in the subsequent dimerization of norbornadiene. The filtration was carried out in an argon-filled glove bag.

Pentacyclo[8.2.1.1.^{4,7}0.^{2,9}0^{3,8}]tetradecanes (70-72)

The procedure used was that reported by Schrauzer and coworkers[116] who carried out the reaction in a sealed tube. We do NOT recommend this method unless the reaction vessel is placed inside a heavy-walled steel apparatus. During our initial experiments an explosion occurred when the reaction was carried out without this precaution. The explosion completely destroyed a blast shield and caused extensive damage to the fume hood in which the reaction was carried out.

A mixture of bicyclo[2.2.1]nona-2,5-diene (375 g, 4.1 M), bisfumaronitrile nickel(0) (10.5 g, 50 mM), and triphenyl phosphine (42 g, 160 mM) was added to an argon-purged pressure bottle (*ca.* 1 l capacity, 5 mm thick walls). The bottle was cooled to 0°, evacuated and sealed. The bottle was then placed inside a stainless steel hydrogenation apparatus and the reaction heated to 100°. After 48 hr the reaction was cooled to room temperature and the hydrogenation apparatus cautiously opened. The pressure bottle was cooled in an ice bath, opened, and pentane (400 ml) was added to the flask. The mixture was vigorously shaken and then filtered through Celite. The filter pad was washed with pentane (2 x 250 ml) and the combined filtrate was concentrated to afford 350 g of a dark brown liquid. Distillation of this residue gave 285 g (76%) of a colourless mixture of dimers (bp 60°, 0.3 mm) consisting mainly (*ca*. 80% as estimated by gas chromatographic analysis) of the *endo-anti-exo* isomer **71**.

This dimeric mixture was formerly available from Aldrich Chemical Company Inc. The pmr spectra of the commercial product and our synthetic dimer are identical.

pmr (CCl_4): τ 3.5-4.1 (m, 4*H*), 7.0-7.5 (m, 4*H*), 7.9-8.5 (m, 4*H*), 8.5-9.0 (m, 4*H*)

glpc: Reoplex, 140°

Bicyclo[4.2.1]nona-2,4,7-triene (69)

An abbreviated account of this preparation has been reported by Cannell.[115] A more detailed description of the reaction conditions is given below.

The pyrolysis of the norbornadiene dimers was carried out in a flow system. The cracking column consisted of a pyrex tube (2.5 x 35 cm) packed with glass beads (3 mm in diameter). The column had a single row of Vigreux indentations at the base in order to support the glass beads. The column was placed vertically into a Lindberg Hevi-Duty pyrolysis oven or was wrapped with "Heat by the Yard" tape and an insulating layer of asbestos cloth. A slow, constant flow of argon (ca. 30 ml/min) was passed downwards through the pyrolysis column and a three-necked receiving flask (-40°). The pyrolysis bed was heated to approximately 400°. The temperature was monitored by the pyrometer attached to the pyrolysis oven or, if the heating tape was used, by a chromel-alumel thermocouple, sheathed in stainless steel and inserted directly into the packed bed. The norbornadiene dimer was introduced by means of a Hershberg dropping funnel at a slow, constant rate (one drop every 6-10 sec; ca. 10 ml/hr) into the argon stream at the top of the pyrolysis column. The condensed effluent was concentrated (20°, 10 mm) to remove cyclopentadiene and fractionally distilled through a 30-cm Vigreux column to afford pure triene 69 (bp 50-52°, 15 mm) in 77% yield.

The flow rate and temperature given above is only a guide since the product distribution is a function of both temperature and contact time. Early cracking fractions should be checked by pmr spectroscopy in order to ensure that aromatic material, characterized by an absorption at τ 2.75, is not present, and that a substantial amount of the dimer is not being recovered. The temperature and/or flow rates are then adjusted to obtain the optimum cracking conditions.

This system allows approximately 1000 g of dimer to be cracked over a four-day period if the pyrolysis is carried out continuously. Each day the pyrolysate was concentrated, combined with the material collected on the previous day, and stored at -30° in order that only one distillation had to be carried out.

pmr (CCl_4): τ 3.68-4.51 (m, 4H), 4.87 (m, 2H), 6.93 (bt, 2H), 8.07 (dt, J_d = 11.5, J_t = 6, 1H), 8.7 (d, J = 11.5, 1H)

glpc: Reoplex, 110°

(±)-exo-Bicyclo[4.2.1]nona-2,4-dien-7-ol (74)

The procedure outlined by Hooz[120b] was followed for the preparation of bis(3-methyl-2-butyl)borane.

A solution of 2-methyl-2-butene (71.5 g, 1.0 M) in anhydrous tetrahydrofuran (100 ml) was added dropwise over 30 min to a cold (5°), stirred solution of diborane (0.93M, 540 ml, 500 mM) in tetrahydrofuran. The solution of dialkylborane was stirred for 3 hr at 5° and then was added dropwise over 35-45 min to a cold (0-5°), stirred solution of bicyclo[4.2.1]nona-2,4,7-triene 69 (55 g, 466 mM) in anhydrous tetrahydrofuran (150 ml). Upon completion of the addition, the mixture was stirred at 0° for 2 hr, and then at room temperature for 18 hr. The reaction mixture was cooled to 0-5° and hydrolysed by first adding aqueous 3N sodium hydroxide (175 ml, 525 mM) in several portions and then aqueous 30% hydrogen peroxide (160 ml, 1500 mM). The hydrogen peroxide was added at such a rate that the temperature of the reaction mixture remained between 30° and 40°. The resulting cloudy mixture was vigorously stirred for 2 hr at room temperature and then extracted with ether (3 x 350 ml). The combined ether extract was washed with water (350 ml) and aqueous saturated sodium chloride (350 ml), dried (Na_2SO_4) and the solvent evaporated. The by-product, 3-methyl-2-butanol, was removed by distillation (bp 110-115°, 760 mm) and the residue was fractionally distilled to give 47.6 g (75%) of 74 as a low-melting crystalline solid (bp 64-70°, 0.2 mm)

ir (CCl_4): 3626 (m), 3348 (bm), 3025 (m), 1597 (w), 1029 (s)

pmr (CCl_4): τ 3.75-4.65 (m, 4H), 5.78 (m, 1H), 6.2 (bs, OH), 7.21 (m, 1H), 7.38-8.78 (m, 5H)

glpc: Reoplex, 170°

Aluminum tri-*tert*-butoxide

The reaction was carried out according to the procedure reported in *Organic Synthesis*.[122] The *tert*-butyl alcohol was distilled from calcium oxide.

Mercury(II) chloride (*ca.* 1 g) was added with vigorous shaking to a gently refluxing mixture of aluminum foil (128 g, 4.74 g-atoms) which had been crumpled into small loose spheres, *tert*-butyl alcohol (400 g, 510 ml, 5.4 M) and aluminum triisopropoxide (10 g). The reaction mixture turned white, and then over 1-2 hr, black. After the reaction mixture had turned black, the heat source was removed and *tert*-butyl alcohol (488 g, 620 ml, 6.6 M) and anhydrous benzene (400 ml) were added. The reaction was initiated again with gentle heating, after which it continued to reflux without any external heating for 2-3 hr. The reaction mixture was then refluxed for 18 hr. The benzene and excess tert-butyl alcohol were distilled off, and anhydrous ether (ca. 2000 ml) was added. The mixture was refluxed briefly to dissolve the product, and after the solution had cooled to room temperature, wet ether (75 ml) was added, followed by vigorous shaking. The mixture was allowed to stand for 2 hr and was then centrifuged. After decanting the supernatant ether, the residual solvent was evaporated and the product was finely ground, and then dried for 5 hr under reduced pressure (0.01 mm) to give 780 g (80%) of a light grey powder.

(±)-Bicyclo[4.2.1]nona-2,4-diene-7-one (75)

a) Oppenauer Oxidation

Commercial 98% 4-benzoquinone was used without further purification. If the quinone is not of this purity it should be recrystallized from hexane or sublimed before use. The quinone must be bright lemon yellow in colour and should not appear at all green The procedure for the Oppenauer oxidation outlined by Wiberg et al.[121a] and by Bly and Bly[121b] was adopted with certain modifications.

Finely powdered aluminum tri-*tert*-butoxide (150 g, 610 mM) was added to a solution of *exo* alcohol **74** (75 g, 550 mM) and 4-benzoquinone (265 g, 2.45 M) in anhydrous ether (3.2 l). When heated to reflux, the solution quickly developed a deep purple colour and a precipitate formed. After refluxing for 24 hr, the mixture was cooled to room temperature and cautiously hydrolysed with aqueous 3*N* hydrochloric acid (500 ml). The ether layer was decanted, and the aqueous phase was extracted with a further 750 ml of ether. The combined ether layer was washed with aqueous 3*N* hydrochloric acid (4 x 250 ml), aqueous 1*N* sodium hydroxide (6 x 250 ml, or until the ether was almost colourless), and aqueous saturated sodium chloride (2 x 250 ml). The ether was evaporated, and the residue was taken up in dichloromethane (500 ml) and dried (Na_2SO_4). Evaporation of the solvent at 5° and flash distillation of the resulting yellow oil gave 55.3 g (75%) of the desired ketone **75** (bp 50°, 0.4 mm).

b) Chromate Oxidation

The procedure for the chromate oxidation outlined by Rao and Filler[123] was used with slight modification.

exo Alcohol **74** (13.6 g, 100 mM) was added to a solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (29.8 g, 100 mM) in dimethylsulphoxide (150 ml). The solution was cooled in an ice bath, and concentrated sulphuric acid (22 ml) was added at such a rate that the reaction temperature remained between 60° and 70°. Upon completion of the addition of the acid, the reaction mixture was heated at 70° for 30 min before being poured into ice/water (600 ml). The aqueous phase was extracted with ether (5 x 500 ml). The ether layer was then dried (Na_2SO_4) and evaporated. Distillation of the residue gave 6.9 g (50%) of the desired ketone.

ir (CCl_4): 3044 (m), 1743 (s), 1596 (m)

pmr (CCl_4): τ 3.67-4.62 (m, 4H), 6.73 (m, 1H), 7.09 (m, 1H), 7.41-8.00 (m, 3H), 8.23 (dt, J_d = 12.5, J_t = 1.6, 1H)

mass spectrum: calcd for $C_9H_{10}O$: m/e = 134.0732

measured: m/e = 134.0728

glpc: Reoplex, 170°

(±)-endo-Bicyclo[4.2.1]nona-2,4-dien-7-ol (76)

A solution of ketone 75 (2.15 g, 16.0 mM) in ether (25 ml) was cooled to -78° and treated with an ether solution (1.64M, 5.5 ml, 9.0 mM) of lithium aluminum hydride. The mixture was stirred for 15 min at 0°, diluted with ether (75 ml), and hydrolysed by the successive addition of water (0.33 ml), aqueous 3N sodium hydroxide (0.50 ml), and water (1.0 ml). After stirring at room temperature for 1 hr the mixture was filtered through Celite. The filter pad was thoroughly washed with ether (50 ml), and the combined filtrate was dried (Na_2SO_4) and the solvent evaporated. The residue was flash distilled to give 1.96 g (90%) of 76 as a white crystalline solid (mp 35.5-37.5°).

ir (CCl_4): 3630 (w), 3582 (m), 3440 (s), 1080 (s)

pmr (CCl_4): τ 3.80-4.60 (m, 4H), 5.73 (dt, $J_d = 8.7$, $J_t = 6.5$, 1H), 7.18 (bq, J = 6, 1H), 7.47 (bq, 1H), 7.64-8.57 (m, 5H)

(±)-Bicyclo[4.2.1]nona-3-formyl-5,7-dien-2-one (77)

A procedure similar to that described by Ainsworth[124] was used. Ethyl formate was dried by distillation from phosphorus pentoxide.

A solution of ketone 75 (62.5 g, 465 mM) and anhydrous ethyl formate (60 ml, 54.5 g, 735 mM) in anhydrous ether (100 ml) was added dropwise over 30 min to a cold (5°), stirred suspension of sodium hydride (50% dispersion in mineral oil, 50 g, 1.04 M) and 98% ethanol (4 ml) in anhydrous ether (1.5 l). The reaction mixture was stirred at room temperature for 18 hr and then treated with a further portion of 98% ethanol (20 ml). After an additional 1 hr stirring, water (400 ml) was added to the reaction mixture. After approximately 10 min, two homogeneous layers formed. The layers were separated and the ether layer washed with water (3 x 250 ml). The combined aqueous solution was washed with ether (3 x 250 ml), cooled to 5°, mixed with dichloromethane (600 ml), and finally acidified to pH 1-2 with aqueous 3N hydrochloric acid. The dichloromethane layer was separated and the aqueous solution extracted with dichloromethane (3 x 400 ml). The combined dichloromethane solution was dried (Na_2SO_4), and the solvent evaporated to give 64.0 g (85%) of crude 77 as a pink solid (mp 112-115°). The product was of sufficient purity for direct use in the subsequent cleavage reaction.

ir ($CHCl_3$): 3600-2500 (bm), 1673 (s), 1600 (s)

pmr (CCl_4): τ 1.07 (bs, 1H), 2.73 (s, 1H), 3.50-4.41 (m, 4H), 6.60 (bt, 2H), 7.35-7.87 (m, 1H), 8.26 (d, J = 11.6, 1H).

cis-Cyclohepta-4,6-diene-1,3-dicarboxylic acid (68)

The procedure for the periodate oxidation reported by Cornforth, Cornforth and Popjak[125b] was followed with certain modifications.

A solution of sodium metaperiodate (121 g, 568 mM) in water (800 ml) was added rapidly to a cold (0-5°), stirred solution of the crude hydroxymethylene ketone 77 (30.2 g, 186 mM) in dioxane (400 ml). Upon completion of the addition of the periodate solution, the cold reaction mixture was diluted with water (800 ml).

Stirring and cooling were maintained for 1 hr during which time aqueous 3N sodium hydroxide (130 ml) was added dropwise to maintain the pH of the reaction mixture at 4.5-5.0. A white precipitate appeared locally where the sodium hydroxide solution was added, and after 20 min a copious precipitate formed in the reaction. The mixture was stirred at room temperature for 4.5 hr, filtered through Celite and the filter pad washed with dioxane (2 x 200 ml). The combined filtrate was concentrated by evaporation to approximately 1500 ml, acidified to pH 1-2 with aqueous 2N sulphuric acid, extracted with ether (1 x 500 ml), saturated with sodium chloride and again extracted with ether (4 x 500 ml). The ether extract was washed with aqueous saturated barium carbonate (250 ml) to remove residual sulphuric acid, and then with aqueous saturated sodium chloride (250 ml). The ether solution was dried ($MgSO_4$) and evaporated to give a brown solid which was suspended in dichloromethane (100 ml) and filtered to afford 32.0 g (94.5%) of diacid **68** as a light yellow granular solid (mp 286-288°, decomp). The pmr of the dimethyl ester of this product contained no signals attributable to the *trans* isomer.[64] An analytical sample was recrystallized from ether-hexane.

ir (KBr): 3600-2000 (bs), 1680 (bs), 1232 (bs), 1250 (bs) pmr: The sample was prepared by suspending the diacid in D_2O (0.5 ml) and adding the minimum amount of a D_2O solution of NaOD to effect the complete dissolution of the diacid. The pH of the solution was 6. An external tetramethylsilane standard was used.

τ 4.00-4.40 (m, 4H), 6.50-6.95 (4, 2H), 7.44-8.33 (m, 2H)

elemental analysis: calcd for $C_9H_{10}O_4$: C 59.33, H 5.54

found: C 59.39, H 5.62

Diazomethane

N-Methyl-N-nitrosourea (10.3 g, 100 mM), purchased from Terochem Co., was added in small portions to a gently stirred mixture of ether (100 ml) and aqueous 50% potassium hydroxide (35 ml) over 1 hr at 0-5°. The deep yellow ether solution was then decanted onto potassium hydroxide pellets and stored at -20° for at least 2 hr in order to dry the solution. The diazomethane concentration (ca. 0.5M) was determined by reaction of an aliquot of the solution with excess benzoic acid, followed by back titration of the unreacted acid with aqueous 0.1N sodium hydroxide.

Dimethyl cis-Cyclohepta-4,6-diene-1,3-dicarboxylate (**66**)

Methanol was added to a suspension of diacid **68** (100 mg, 0.55 mM) in ether (2 ml) until the acid dissolved. After treatment with excess ethereal diazomethane, the solvent was evaporated, the oil dissolved in dichloromethane (2 ml) and dried ($MgSO_4$). Evaporation of the solvent gave 116 mg (100%) of **66** as a colourless oil. No signals attributable to the trans-diester[64] were observable in the pmr spectrum.

ir ($CHCl_3$): 1740 (s), 1437 (m)

pmr ($CDCl_3$): τ 3.80-4.36 (m, 4H), 6.28 (s, 6H) 6.50 (cd, J ≈ 10, 2H), 7.47 (cdt, J_d = 13.5, J_t = 3.6, 1H), 7.82 (dt, J_d = 13.5, J_t = 11.5, 1H).

glpc: UCW-98, 190°

Purification of Copper(I) Iodide

The procedure of Kauffman and Teter[158] was used.

Commercial copper(I) iodide (225 g) was dissolved in aqueous saturated potassium iodide (2260 g KI in 1750 ml of water), and the resulting brown solution shaken with decolourising carbon (ca. 10 g) for 10 min. The mixture was filtered through Celite and the yellow filtrate diluted with water (5000 ml) to produce a copious precipitate which was collected by filtration. The copper(I) iodide was washed with water (4 x 250 ml), reagent acetone (4 x 250 ml) and anhydrous ether (4 x 250 ml), and finally dried at room temperature under reduced pressure (0.01 mm) for 18 hr to yield 169 g (75%) of a very pale yellow solid. The purified copper(I) iodide is stable for several months if it is protected from the atmosphere.

(±)-Dimethyl 4,5-Epoxycyclohept-6-ene-1,3-dicarboxylate (**81**)

A solution of diacid **68** (10.0 g, 55 mM) in dichloromethane (300 ml) and anhydrous tetrahydrofuran (120 ml) was treated with a solution of 3-chloroperbenzoic acid (85%, 13.2 g, 64.5 mM) in dichloromethane (250 ml). After stirring for 24 hr the solution was cooled to 0° and esterified with an excess of ethereal diazomethane. The solvent was evaporated and the residue dissolved in dichloromethane (150 ml) and dried (Na_2SO_4). Removal of the solvent then afforded a mixture of epoxides **81** and methyl 3-chlorobenzoate as a colourless liquid which was used immediately in the next reaction.

(±)-Methyl 4-Methyl-7-oxo-6-oxabicyclo[3.2.2]non-2-ene-9-carboxylate (86)

In preparation for this reaction, all traces of water were removed from the mixture of moneopoxides 81 by coevaporation with anhydrous xylene at room temperature.

An ether solution of methyllithium (1.6M, 35 ml, 220 mM) was added over 10 min to a stirred suspension of purified copper(I) iodide (21 g, 110 mM) in anhydrous ether (500 ml) at -30°. During the addition, a yellow precipitate of methylcopper appeared which dissolved as the second equivalent of methyllithium was added, to afford a pale tan solution. The lithium dimethylcuprate solution was stirred at -30° for an additional 30 min, and then a solution of the crude monoepoxides 81 in anhydrous ether (200 ml) was added over 5 min. The resulting yellow suspension was stirred at -20° for 1.5 hr before it was quenched with aqueous saturated ammonium chloride (500 ml). The reaction mixture was stirred for 30 min at 10-20°, the ether layer decanted and the aqueous layer extracted with ether (4 x 100 ml). [The colourless aqueous layer rapidly became deep blue when exposed to air.] The combined ether solution was washed with aqueous saturated sodium chloride (2 x 100 ml). The solvent was evaporated, and the residue dissolved in dichloromethane (100 ml) and dried (Na_2SO_4). Evaporation of the solvent, followed by chromatography of the yellow residue on silicic acid (500 g, chloroform) afforded the desired lactone as a white solid. Recrystallization from cyclohexene gave 3.12 g (27%) of pure **86** (mp 65-68°) based on the starting diacid.

ir ($CHCl_3$): 1741 (s)

pmr ($CDCl_3$): τ 4.19 (ddd, J = 10.5, 2.2, 1*H*),
4.48 (ddt, J_d = 10.5, 0.9, J_t = 1.5, 1*H*),
5.22 (cdd, J = 3.7, 1.0, 1*H*), 6.25
(s, 3*H*), 6.73-7.20 (m, 3*H*), 7.51 (m, 2*H*),
8.87 (d, J = 7.3, 3*H*)

elemental analysis: calcd for $C_{11}H_{14}O_4$: C 62.84, H 6.71
found: C 62.83, H 6.80

glpc: UCW-98, 210°

(±)-3*R*,5*R*-Dihydroxymethyl-6*R*-hydroxy-7*S*-methylcyclohept-1-ene (**88**)

A solution of lactone **86** (10.5 g, 50 mM) in anhydrous tetrahydrofuran (150 ml) was treated at 0° with a tetrahydrofuran solution (1.0*M*, 200 ml, 200 mM) of lithium aluminum hydride. The milky white suspension was gently refluxed for 18 hr, cooled to 0° and cautiously hydrolysed with aqueous tetrahydrofuran. The mixture was then stirred at room temperature for 1.5 hr, filtered through Celite, and the filter pad washed with anhydrous tetrahydrofuran (4 x 100 ml). The combined filtrate was evaporated and the residue dissolved in methanolic chloroform (1% by volume, 100 ml) and dried (Na_2SO_4-$MgSO_4$, 1:1 by weight). Evaporation of the solvent gave 9.3 g (100%) of triol 88 as a colourless glass. The triol was converted into 89 without further purification.

(±)-3*R*,5*R*-Di(4-toluenesulphonyloxymethyl)-6*R*-hydroxy-7*S*-methylcyclohept-1-ene (89)

In preparation for this reaction, trace amounts of water were removed from triol 88 by coevaporation with anhydrous pyridine at room temperature.

A solution of triol 88 (9.3 g, 50 mM) and 4-toluenesulphonyl chloride (19.1 g, 101 mM) in anhydrous pyridine (125 ml) was stored at 0° for 24 hr. The mixture was concentrated under reduced pressure (0.01 mm) to approximately 25 ml, poured into cold (5-10°) aqueous 1*N* hydrochloric acid (200 ml) and extracted with ether (4 x 125 ml). The combined ether extract was successively washed with aqueous 1*N* hydrochloric acid (2 x 100 ml), water (2 x 75 ml), and aqueous saturated sodium chloride (75 ml). The ether was evaporated and the residue dissolved in dichloromethane (150 ml) and dried (Na_2SO_4). Removal of the solvent gave 21.7 g (88%) of oily 89.

This compound is unstable towards silicic acid chromatography and was used directly in the next reaction.

ir ($CHCl_3$): 3570 (bm), 3035 and 3010 (m), 1600 (m), 1360 (s), 1178 and 1190 (s)

pmr ($CDCl_3$): τ 2.10-2.86 (m, 8H), 4.41-4.64 (m, 2H), 5.86-6.39 (m, 5H), 7.30-8.40 (m, 9H), 8.70 (m, 2H), 9.04 (d, J = 7, 3H), 7.55 (s, aryl-CH_3)

mass spectrum: calcd for $C_{17}H_{22}O_4{}^{32}S$ (P-TsOH): m/e = 322.1239

measured: m/e = 322.1245

(±)-3R,5R-Di(4-toluenesulphonyloxymethyl)-6R-acetoxy-7S-methylcyclohept-1-ene (90)

A solution of alcohol 89 (494.6 mg, 1.0 mM) and acetic anhydride (615 mg, 6.0 mM) in anhydrous pyridine (2.0 ml) was stored at 0° for 48 hr. The solvent was then removed under reduced pressure (0.01 mm). The residue was dissolved in benzene-pentane (1:1, 25 ml), washed with aqueous 1N hydrochloric acid (5 ml) and aqueous saturated sodium chloride (5 ml), and dried (Na_2SO_4). Removal of the solvent afforded a pale yellow viscous oil which slowly solidified. Recrystallization from ether-hexane (1:1) gave 467 mg (87%) of 90 as fine white crystals (mp 114-115°).

ir ($CHCl_3$): 1738 (s), 1602 (m), 1370 (bs), 1100 (s)
1024 (m), 975 (bs)

pmr (CCl_4): τ 2.17-2.61 (m, 8H), 4.28-4.88 (m, 2H),
4.90-5.22 (m, 1H), 6.1 (m, 4H),
7.15-7.90 (m, 9H), 8.06 (s, 3H),
8.36-8.87 (m, 2H), 9.05 (d, J=7, 3H)
τ 7.52 (s, aryl-CH_3)

elemental analysis: calcd for $C_{26}H_{32}O_8S_2$: C 58.19, H 6.01
found : C 58.65, H 6.20

Reaction of 90 with lithium dihydrocuprate

An ether solution (1.6M, 3.75 ml, 6.0 mM) of methyllithium was added to a stirred suspension of purified copper(I) iodide (570 mg, 3.0 mM) in anhydrous ether (10 ml) at -30°. To the pale yellow solution of lithium dimethylcuprate was then added, with stirring, an ether solution (0.3M, 10 ml, 3.0 mM) of lithium aluminum hydride, and the solution allowed to warm to room temperature. As the reaction mixture warmed, a bright yellow precipitate appeared. After 10 min at room temperature, the stirring was stopped and the supernatant ether removed by syringe. Fresh ether (25 ml) was added, the reaction stirred for 1 min, and the ether again replaced with fresh anhydrous ether.

Ditosyl acetate 90 (268 mg, 0.50 mM) was added to the cuprate solution and the reaction stirred at room temperature for 2 hr. The reaction was then quenched with aqueous saturated ammonium chloride (5 ml) and the ether solution dried (Na_2SO_4) and evaporated to give 70 mg (92%) of 91 as a colourless oil. This compound is identical to the material obtained by reaction of 90 with lithium aluminum hydride.

pmr (CCl_4): τ 3.95-4.8 (m, 2*H*), 6.0 (m, 2*H*)
6.65 (bt, J = 1.5, 1*H*), 6.9-7.4 (m, 1*H*),
7.5-8.3 (m, 3*H*), 8.4-8.7 (m, 1*H*),
8.95 (t, J = 7.2, 6*H*)

mass spectrum: 152 (P)

glpc: UCW-98, 140°

(+)-3*R*,5*R*-Di(4-toluenesulphonyloxymethyl)-6*R*-trimethylsiloxy-7*S*-methylcyclohept-1-ene (98)

A solution of ditosyl alcohol 89 (11.2 g, 25 mM) in anhydrous pyridine (100 ml) was treated with freshly distilled trimethylchlorosilane (6.75 g, 62.5 mM). The mixture was stirred at room temperature for 2 hr before the solvent was removed under reduced pressure (0.01 mm). The residue was taken up in ether (200 ml) and washed with water (50 ml), aqueous 1*N* hydrochloric acid (25 ml), and aqueous saturated sodium chloride (25 ml). The ether was then dried (Na_2SO_4) and evaporated to give 13.9 g (98%) of **98** as a colourless oil which was used immediately in the next reaction.

pmr (CCl_4): τ 2.1-2.8 (m, 8H), 4.5-4.8 (m, 2H),
5.9-6.4 (m, 4H), 7.3-8.3 (m, 10H),
8.7-9.2 (m, 5H), 10.0 (s, 9H)
τ 7.6 (s, aryl-CH_3)

mass spectrum: calcd for $C_{17}H_{22}O_4{}^{32}S$ [P-(TsOH and $OSiMe_3$)]:
m/e = 322.1239
measured: m/e = 322.1240

(±)-4S-Trimethylsiloxy-3S,5S,7R-trimethylcyclohept-1-ene (99)

A solution of silyl ether **98** (2.84 g, 5.0 mM) in anhydrous ether (50 ml) was added to a stirred suspension of lithium dihydrocuprate (30 mM, 6 equiv) prepared as above. After 18 hr at room temperature the reaction mixture was worked up. The dried (Na_2SO_4) solvent was evaporated at 0°. The pmr spectrum of the crude product indicated a ratio of desired product to tosylate-containing material of approximately 9:1. The residue was distilled through a short-path apparatus to give 975 mg (86%) of pure **99** (bp 45°, 0.1 mm).

pmr (CCl_4, $CHCl_3$ reference): τ 4.6 (d, J = 1.5, 2*H*),
6.35 (dd, J = 1.5, 1.8, 1*H*),
7.4-7.8 (m, 2*H*), 7.8-8.2
(m, 1*H*), 8.2-8.8 (m, 2*H*),
8.92 (d, J = 7, 3*H*),
8.98 (d, J = 7.5, 3*H*),
9.05 (d, J = 7, 3*H*),
9.8 (s, 9*H*)

mass spectrum: calcd for $C_{13}H_{26}O^{28}Si$: m/e = 226.1753
measured: m/e = 226.1748

glpc: UCW-98, 140°

(±)-4*S*-Hydroxy-3*S*,5*S*,7*R*-trimethylcyclohept-1-ene (**100**)

With stirring, concentrated hydrochloric acid (5 drops) was added to a solution of silyl ether **99** (1.13 g, 5.0 mM) in anhydrous methanol (100 ml). After 15 min at room temperature, solid sodium bicarbonate (*ca*. 0.5 g) was added, and the mixture concentrated to approximately 5 ml at 0°. The residue was diluted with ether (200 ml) and washed with water (2 x 10 ml) and aqueous saturated sodium chloride (2 x 10 ml). The ether was dried (Na_2SO_4) and evaporated at 0° to give 776 mg (98%) of pure **100**.

ir (CCl_4): 3632 (w), 3581 (m), 3490 (bm), 3010 (m),
1455 (s), 1376 (s), 994 (s)

pmr ($CDCl_3$): τ 4.48 (m, 2H), 6.43 (dd, J = 2.0, 6.0, 1H)
7.41 (bm, 1H), 7.65 (bm, 1H), 7.96 (bm, 1H)
8.16 (bs, 1H), 8.71 (m, 2H), 8.94 (d,
J = 7.2, 3H), 8.97 (d, J = 7.2, 3H)
8.98 (d, J = 7, 3H)

mass spectrum: 154 (P)

glpc: UCW-98, 140°

(±)-4S-Acetoxy-3S,5S,7R-trimethylcyclohept-1-ene (96)

A solution of alcohol 100 (1.54 g, 10.0 mM) and acetic anhydride (6.15 g, 60 mM) in anhydrous pyridine (20 ml) was heated at 40° for 24 hr. After cooling to room temperature, the mixture was concentrated under reduced pressure (0.01 mm) to approximately 5 ml, poured into cold (5-10°) aqueous 1N hydrochloric acid (50 ml) and extracted with benzene-pentane (1:1 by volume, 4 x 50 ml). The combined extract was washed successively with aqueous 1N hydrochloric acid (2 x 20 ml), aqueous saturated sodium bicarbonate (20 ml), water (20 ml), and aqueous saturated sodium chloride (20 ml). After drying (Na_2SO_4), the solvent was evaporated at 0°, and the residue flash distilled to give 1.92 g (98%) of 96 as a colourless liquid (bp 76-80°, 3.5 mm).

ir (CCl_4): 3012 (w), 1735 (s), 1459 (m), 1247 (s)

pmr ($CDCl_3$): τ 4.67 (m, 2H), 5.17 (dd, J = 3.1, 6.6, 1H), 7.15-8.19 (m, 6H), 8.61 (m, 2H), 8.82-9.22 overlapping doublets, 9H), 8.06 (s, CH_3CO)

mass spectrum: calcd for $C_{10}H_{16}$(P-HOAc): m/e = 136.1252

measured: m/e = 136.1249

glpc: Reoplex, 180°

(±)-3S-Acetoxy-2R,4S,6R-trimethylheptan-1,7-dioic acid (101)

A solution of trimethylcycloheptenyl acetate 96 (450 mg, 2.3 mM) in aqueous 80% tert-butyl alcohol (300 ml) was added to an oxidizing solution (pH 8.5) of potassium permanganate (110 mg, 0.70 mM), sodium metaperiodate (5.74 g, 26.9 mM), and anhydrous potassium carbonate (5.0 g, 36.4 mM) dissolved in water (300 ml). The mixture was vigorously stirred at room temperature for 24 hr, before the red-purple solution was acidified to pH 3.5 with aqueous 4N sulphuric acid (20 ml). Solid sodium bisulphite (ca. 10 g) was slowly added to reduce the remaining oxidant. During this addition the solution first became colourless, then dark brown, and finally bright yellow. The pH of the solution was now 1.5. The solution was adjusted to pH 7.0 with aqueous 2N sodium hydroxide (55 ml), concentrated to approximately 250 ml, and the pH raised to 9-9.5 with aqueous 2N sodium hydroxide (ca. 1 ml). The yellowish concentrate was washed with ether (2 x 40 ml), acidified to pH 1.5 with aqueous 4N sulphuric acid (15 ml), carefully saturated with sodium chloride (sulphur dioxide from excess sodium bisulphite was evolved), and extracted with ether (5 x 50 ml). The combined ether extract was washed with aqueous saturated sodium chloride (50 ml), dried (Na_2SO_4) and evaporated to give a very pale yellow viscous oil which slowly solidified on standing. Recrystallization from ether-hexane gave 510 mg (86%) of pure acetoxy diacid 101 as white prisms (mp 110-111°).

ir ($CHCl_3$): 3600-2400 (bm), 1735 (m), 1710 (s),
1240-1210 (bm).

pmr ($CDCl_3$): τ -2.24 (bs, 2H), 4.86 (dd, J = 1.7, 11.0, 1H), 7.13 (qd J_q = 7, J_d = 11, 1H), 7.47 (bm, 1H), 7.79-8.69 (m, 6H), 8.76 (d, J = 7.0, 3H), 8.80 (d, J = 7.0, 3H) 9.04 (d, J = 6.6, 3H)

mass spectrum: calcd for $C_{12}H_{20}O_6$: m/e = 260.1260
measured: m/e = 260.1255

elemental analysis: calcd for $C_{12}H_{20}O_6$: C 55.37, H 7.74
found : C 55.46, H 7.61

(±)-3*S*-Hydroxy-2*R*,4*S*,6*R*-trimethylheptan-1,7-dioic 3,7-lactone (**6**) [(±)-Djerassi-Prelog lactonic acid]

a) From **101**

A solution of diacid **101** (645 mg, 2.5 mM) in aqueous 1.6*N* potassium hydroxide (6.25 ml, 10.0 mM) was stirred at room temperature for 18 hr. The mixture was cooled to 0° and carefully acidified to pH 1.5 by the dropwise addition of aqueous 2*N* hydrochloric acid. The mixture was then saturated with sodium chloride and stirred for 30 min at 0° before being extracted with chloroform (3 x 25 ml). The combined chloroform layer was washed with aqueous saturated sodium chloride (20 ml), dried (Na_2SO_4) and evaporated to give 501 mg (100%) of chromatographically pure **6** as white prisms (mp 112-113°, 119-120°). An analytical sample was recrystallized from ether-pentane.

b) Direct cleavage of **99**

A solution of silyl ether **99** (521 mg, 2.3 mM) was subjected to the Lemieux-von Rudloff oxidation as described above. After 40 hr at room temperature the red-purple solution was worked up using the procedure outlined above. The acidic aqueous phase was extracted with ether (7 x 50 ml). The ether was dried (Na_2SO_4) and evaporated to give a pale yellow solid. Recrystallization from ether-pentane gave 400 mg (87%) of **6** as white prisms (mp 119-120°).

ir ($CHCl_3$): 3600-2400 (bm), 1725 (s), 1460 (m), 1382 (m)
1189 (m), 1100 (m)

pmr ($CDCl_3$): τ 1.30 (bs, 1*H*), 5.42 (dd, J = 2.4, 10, 1*H*),
7.26 (qd, J_q = 7.1, J_d = 2.4, 1*H*),
ca. 7.51 (m, 1*H*), 7.86-8.33 (m, 2*H*),
8.33-8.62 (m, 1*H*), 8.72 (d, J = 6.9, 3*H*),
8.81 (d, J = 7.2, 3*H*), 8.99 (d, J = 6.4, 3*H*)

cmr ($CDCl_3$), ORD multiplicity, assignment: δ 8.42 (d, C-6),
16.94 (q, C_6-CH_3), 17.21 (q, C_4-CH_3), 30.97
(q, C_2-CH_3), 36.31 (d, C_4), 37.28 (t, C_5),
41.16 (d, C_2), 86.42 (d, C_4), 174.63 (s, C_7),
177.75 (s, C_1)

elemental analysis: calcd for $C_{10}H_{16}O_4$: C 59.88, H 8.03
found : C 59.56, H 8.05

(±)-Methyl Hydrogen 3*S*-Hydroxy-2*R*,4*S*,6*R*-trimethylheptan-1,7-dioate 3,7-lactone (**25**)

A solution of lactonic acid **6** (400 mg, 2.0 mM) in dichloromethane (10 ml) was treated with an excess of ethereal diazomethane at 0°. Evaporation of the solvent afforded 428 mg (100%) of gas chromatographically pure **25** as a white crystalline powder. Recrystallization from ether-pentane gave 406 mg (95%) of 25 as white prisms (mp 73-74°, sublimable at 80°, 2 mm).

ir (CCl_4): 1735 (s)

pmr (CCl_4): τ 5.61 (dd, J = 9.5, 3.2, 1H), 6.28 (s, 3H)
7.1-7.75 (m, 2H), 7.75-8.6 (m, 3H),
8.77 (d, J = 7.0, 3H), 8.81 (d, J = 7.0, 3H),
8.99 (d, J = 6.0, 3H)

glpc: UCW-98, 200°

(*E*)-2-Methyl-2-pentenal (**102**)

This experiment was carried out according to the procedure outlined by Evans *et al*.[142]

Freshly distilled propanal (145 g, 2.5 M) was added dropwise with vigorous stirring to aqueous 1*N* sodium hydroxide (80 ml) over 45 min. The mixture became warm and slightly yellow in colour. After the stirring was stopped, the mixture separated into two layers. The upper organic layer was drawn off, washed with water (2 x 25 ml) and aqueous saturated sodium chloride (2 x 25 ml), dried (Na_2SO_4) and fractionally distilled to give 78 g (64%) of pure **102** (bp 48-50°, 30 mm).

ir (CCl_4): 1685 (s), 1640 (m)

pmr (CCl_4): τ 1.7 (s, 1*H*), 3.57 (tq, J_t = 8, J_q = 1, 1*H*),
7.60 (qu, J = 7.5, 2*H*), 8.27 (d, J = 1, 3*H*),
8.86 (t, J = 7.5, 3*H*)

glpc: UCW-98, 75°

(*E*)-2-Methyl-2-pentenol

A solution of aldehyde **102** (3.14 g, 32 mM) in anhydrous ether (100 ml) was treated at 0° with an ether solution (1.0*M*, 10 ml, 10 mM) of lithium aluminum hydride. After 30 min the reaction was carefully hydrolysed with wet ether. The mixture was stirred at room temperature for 1 hr, filtered through Celite, and the filter pad washed with ether (2 x 50 ml). The combined filtrate was dried ($MgSO_4$) and the solvent evaporated. The residue was distilled to give 2.95 g (92%) of the alcohol as a colourless oil (bp 68°, 20 mm). Distillation at atmospheric pressure results in dehydration of the product.[142]

pmr (CCl_4): τ 4.7 (bt, J ≈ 7, 1H), 5.7 (bs, 1H), 6.2 (bs, 2H), 8.0 (qu, J = 7, 1H), 8.4 (s, 3H), 9.05 (t, J = 7, 3H)

glpc: UCW-98, 85°

(±)-2,3-Epoxy-2-methylpentanol

3-Chloroperbenzoic acid (85%, 12.2 g, 60 mM) was added to a solution of the above alcohol (5.01 g, 50 mM) in dichloromethane (250 ml) at 0°. After 15 min the reaction mixture was cooled to -78° to precipitate the 3-chlorobenzoic acid and the mixture was filtered (-78°). The filtrate was concentrated, diluted with pentane (75 ml) and left to stand at -20° for 12 hr. The mixture was again filtered. The filtrate was evaporated and the residue was chromatographed on alumina (150 g, pentane-ether 1:1) to give 5.0 g (86%) of epoxy alcohol.

pmr (CCl_4): τ 6.5 (s, 2H), 7.2 (t, J = 7, 1H), 8.5 (qu, J = 7, 2H), 8.8 (s, 3H), 9.0 (t, J = 7, 3H)

glpc: UCW-98, 85°

(±)-2,3-Epoxy-2-methylpentanal (**103**)

Chromium trioxide (30.0 g, 300 mM) was added to an anhydrous solution of pyridine (48 ml, 600 mM) and dichloromethane (350 ml) at 0°. The deep burgundy solution was stirred at 0° for 5 min and was then allowed to warm to room temperature over 1 hr. A solution of the above epoxy alcohol (2.90 g, 25 mM) in dichloromethane (20 ml) was rapidly added. The reaction mixture was stirred for 15 min and then the dichloromethane was decanted from the tarry residue which was washed with ether (3 x 200 ml). The combined ether-dichloromethane solution was stored for 18 hr at -30°. The cold solution was again decanted from a tarry residue, and was then concentrated at 0° to approximately 50 ml. This solution was diluted with pentane (300 ml) and filtered through sodium sulphate to remove some insoluble coloured impurities. With vigorous stirring, excess solid nickel(II) chloride was added to the cold (-78°) pentane solution and the mixture slowly warmed to 0°. This treatment removed the pyridine as an insoluble nickel complex. The pentane solution was filtered and the solvent removed at 0°. The residue was flash distilled to give 1.80 g (63%) of **103** (bp 42°, 10 mm).[144]

ir (CHCl$_3$): 1750 (s)

pmr (CDCl$_3$): τ 1.14 (s, 1H), 6.95 (t, J = 6, 1H),
8.4 (qu, J = 6, 2H), 8.7 (s, 3H), 8.95
(t, J = 6, 3H)

glpc: UCW-98, 85°

Triphenyl(acetylmethylene) Phosphorane

The reaction was carried out according to the procedure reported by Ramirez.[138]

A solution of triphenylphosphine (20.0 g, 76.2 mM) and 1-chloropropan-2-one (6.5 g, 70.2 mM) in chloroform (60 ml) was refluxed for 80 min. The mixture was then filtered into anhydrous ether (600 ml) and the resulting copious precipitate collected by filtration to give 15.9 g (64%) of cream coloured phosphonium salt (mp 241-245°).

The phosphonium salt (15.9 g, 44.5 mM) was dissolved in water (400 ml) and aqueous 1N sodium hydroxide (500 ml) was added rapidly. The resulting precipitate was collected by filtration, washed with water until neutral (ca. 400 ml was required), and finally dried under reduced pressure (0.01 mm) to give 13.1 g (89%) of the phosphorane as a white powder (mp 202-205°).

pmr (CDCl$_3$): τ 2.1-2.8 (m, 15H), 6.30 (bd, J = 27, 1H),
7.93 (d, J = 1.5, 3H)

5-Methylocta-3(*E*),5(*E*)-dien-2-one (**104**)

A solution of aldehyde **102** (3.92 g, 40.0 mM) and triphenyl(acetylmethylene) phosphorane (6.58 g, 20 mM) in anhydrous benzene (100 ml) was refluxed for 40 hr. The solvent was evaporated and the residue was triturated with pentane (5 x 75 ml). The combined pentane extract was filtered and evaporated to give 3.61 g of an orange oil which was chromatographed on silicic acid (175 g, chloroform) to give 1.80 g (65%) of **104** as a pale yellow oil.

ir (CCl_4): 3040 (sh), 1695, 1675

pmr (CCl_4): τ 2.79 (d, J = 16.5, 1*H*), 3.98 (d, J = 16.5, 1*H*), 4.08 (bt, J = 7.5, 1*H*), 7.78 (q, J = 7.5, 2*H*), 7.80 (s, 3*H*), 8.20 (bs, 3*H*), 8.95 (t, J = 7.5, 3*H*)

glpc: UCW-98, 120°

(±)-5,6-Epoxy-5-methyloct-3(*E*)-en-2-one (**105**)

A solution of dienone **104** (280 mg, 2.03 mM) and 3-chloroperbenzoic acid (85%, 416 mg, 2.05 mM) in dichloromethane (7.5 ml) was stirred at room temperature for 40 hr. The reaction mixture was diluted with ether (25 ml), washed with aqueous saturated sodium bicarbonate (4 x 10 ml) and aqueous saturated sodium chloride (10 ml), and was then dried (Na_2SO_4). The solvent was evaporated and the residue molecularly distilled (110°, 1 mm) to give 175 mg (56%) of 105 as a clear colourless oil.

The same product was obtained directly in 52% yield by reaction of epoxy aldehyde 103 and the phosphorane under the conditions used to synthesize 104.

ir (CCl_4): 1680 (s), 1635 (s), 980, 880

pmr ($CDCl_3$): τ 3.38 (d, J = 16.5, 1H), 3.78 (d, J = 16.5, 1H), 7.18 (t, J = 6.5, 1H), 7.75 (s, 3H), 8.38 (m, 2H), 8.57 (s, 3H), 8.06 (t, J = 7, 3H)

glpc: UCW-98, 140°

(±)-5,6-Dihydroxy-5-methyloct-3(E)-en-2-one (106)

Aqueous 2.0N sulphuric acid (1.62 ml, 3.24 mM) was added to a stirred solution of epoxide 105 (250 mg, 1.62 mM) in tetrahydrofuran (5 ml) at 0°. The mixture was then stirred at room temperature for 30 hr, cautiously neutralized with aqueous saturated sodium bicarbonate, diluted with aqueous saturated sodium chloride (10 ml) and extracted with chloroform (3 x 25 ml). The organic phase was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silicic acid (7.5 g, chloroform) to give 220 mg (80%) of 106 as a colourless oil.

ir (CCl_4): 3450 (bs), 1680 (s), 980

pmr (CCl_4): 3.40 (d, J = 16, 1H), 3.76 (d, J = 16, 1H), 6.4-6.8 (m, 1H), 7.35 (bs, 2 OH), 7.72 (s, 3H), 8.1-9.2 (cm, 8H)

(E)-2-Methyl-2-pentenoic acid (113)

This and the following three experimental procedures were carried out according to the method described by Bergel'son and coworkers.[141]

A solution of silver nitrate (260 g, 1.53 M) in water (500 ml) was added rapidly with stirring to a solution of aldehyde 102 (50 g, 510 mM) in ethanol (200 ml). The temperature was raised to 40° and aqueous 3N sodium hydroxide (800 ml, 2.4 M) was added over 3 hr. After the addition was complete, the reaction was maintained at 40° for 18 hr before the mixture was filtered to remove the precipitated silver. The filtrate was acidified to pH 1 with aqueous 6N hydrochloric acid and extracted with ether (5 x 250 ml). The combined ether layer was concentrated to 500 ml, extracted with aqueous 8N sodium hydroxide (3 x 75 ml), and the alkaline extract acidified to pH 1 with aqueous 6N hydrochloric acid. The aqueous phase was then extracted with ether (5 x 100 ml). The ether layer was dried ($MgSO_4$) and evaporated. The residue was distilled to give 48 g (85%) of crude 113 (bp 112-115°, 17 mm) which was dissolved in hexane (100 ml) and the solution cooled to -40°. The crystalline precipitate was collected by filtration at 0° to give 44 g (76%) of pure 113 (mp 23-24°).

ir (CCl_4): 3500-2300 (bs), 1700 (s), 1640 (m)

pmr (CCl_4): τ -0.8 (s, 1H), 3.1 (dt, J = 7, 1.5, 1H), 7.8 (qu, J = 7, 2H), 8.15 (s, 3H), 8.95 (t, J = 7, 3H)

(±)-2*R*,3*R*-Dihydroxy-2*R*-methylpentanoic acid (**115**)

To a solution of acid **113** (16.2 g, 142 mM) in acetic acid (80 ml) was added concentrated sulphuric acid (18 drops) and 70% hydrogen peroxide (14 ml). The reaction mixture was maintained at 50° for 6 hr and then left at room temperature for 18 hr. Sulphur dioxide was bubbled through the cold (0°) solution to reduce the excess hydrogen peroxide. The solvent was then removed under reduced pressure (0.01 mm) and the residue refluxed for 1 hr with aqueous 5*N* sodium hydroxide (100 ml). The mixture was cooled to room temperature and extracted with ether (2 x 25 ml). The aqueous layer was acidified to pH 1 with aqueous 3*N* hydrochloric acid and continuously extracted with ether for 18 hr. The ether extract was dried ($MgSO_4$) and evaporated. The residue was recrystallized from ethyl acetate to give 10.5 g (50%) of pure **115** (mp 153-154°).

pmr (acetone-d_6): τ 4.77 (bs, 3*H*), 6.75 (t, $J = 6.6$, 1*H*),
8.50 (dq, $J_q = 7.7$, $J_d = 6.6$, 2*H*),
8.61 (s, 3*H*), 9.03 (t, $J = 7.7$, 3*H*)

(+)-2*R*,3*R*-Dihydroxy-2*R*-methylpentanoic acid (**115**)

Finely ground racemic acid **115** (31.4 g, 212 mM) was added in one portion to a refluxing solution of *L*-(+)-*threo*-2-amino-1-(4-nitrophenyl)-1,2-propanediol (45.0 g, 212 mM) in ethanol (150 ml). The solution was left to stand at room temperature for 18 hr, and the precipitated salt was collected and recrystallized from ethanol to give 34 g of the [(+)base·(+)acid] salt (mp 156-158°).

Aqueous 14% ammonium hydroxide (160 ml) was added to a solution of the above salt (34 g, 94 mM) in water (240 ml). The reaction mixture was filtered to recover 14.4 g of optically active amine. The filtrate was acidified to pH 1 with aqueous 6*N* hydrochloric acid and continuously extracted with ether for 5 days to give 13.7 g (98%) of crude diol acid 115. Recrystallization from ethyl acetate gave 13.5 g of 115 (mp 149-151°), $[\alpha]_D^{25}$ + 13.1° (*c* 3.02, H_2O) (95% optically pure based on ref 141).

pmr: see racemate above

(+)-Methyl 2*R*,3*R*-Dihydroxy-2*R*-methylpentanoate (116)

An ether solution of diazomethane was added dropwise to a solution of acid (+)-115 (6.86 g, 46 mM) in ether (200 ml) at 0°. The addition was stopped when the reaction mixture became yellow. The solvent was evaporated and the residue distilled to give 7.15 g (100%) of methyl ester 116 (bp 60°, 1.6 mm), $[\alpha]_D^{25}$ ~0°, (*c* 0.66, $CHCl_3$). The (-)-enantiomer of this compound was not detected in the pmr spectrum when the chiral shift reagent tris(3-heptafluoropropylhydroxymethylene-*d*-camphorato) europium(III) was added.

ir (CCl_4): 3500 (bs), 1735 (s)

pmr ($CDCl_3$): τ 6.19 (s, 3H), 6.47 (t, J = 6.5, 1H),
8.35-8.7 (m, 3H), 8.6 (s, 3H),
9.0 (t, J = 6, 3H)

glpc: UCW-98, 100°

(+)-Methyl 2R-Hydroxy-3R-(4-toluenesulphonyloxy)-2R-methylpentanoate (117)

4-Toluenesulphonyl chloride (9.11 g, 43 mM) was added to a solution of dihydroxy ester 116 (5.13 g, 31 mM) in anhydrous pyridine (45 ml) at 0°. The reaction mixture was stirred at room temperature for 18 hr, poured into cold (0°) water (400 ml) and extracted with ether (4 x 75 ml). The combined ether layer was washed with aqueous 1N hydrochloric acid (5 x 100 ml), aqueous saturated sodium bicarbonate (100 ml), and aqueous saturated sodium chloride (100 ml). The ether solution was dried (Na_2SO_4) and evaporated to give 8.32 g (83%) of 117 as a colourless oil, $[\alpha]_D^{22}$ + 13.0° (c 3.08, $CHCl_3$).

ir (film): 3520 (bs), 1740 (s)

pmr ($CDCl_3$): τ 2.1-2.8 (m, 4H), 5.2 (dd, J = 6, 1.5, 1H),
6.2 (s, 3H), 7.6 (s, 3H), 8.35 (m, 2H),
8.6 (s, 3H), 9.1 (t, J = 7, 3H)

(-)-Methyl 2R,3S-Epoxy-2R-methylpentanoate (118)

Freshly distilled triethylamine (8 ml) was added to a solution of tosylate 117 (19.3 g, 61 mM) in anhydrous benzene (25 ml), and the reaction was refluxed for 2.5 hr. Most of the solvent was evaporated and the residue was poured into cold (0°) water (150 ml). The mixture was extracted with ether (3 x 75 ml), and the ether layer washed with aqueous 1N hydrochloric acid (2 x 50 ml), aqueous saturated sodium bicarbonate (50 ml), and aqueous saturated sodium chloride (50 ml). The ether was dried (Na_2SO_4) and evaporated to give 11.3 g of crude epoxy ester. Distillation of this material gave 7.9 g (90%) of pure 118 (bp 65°, 20 mm), $[\alpha]_D^{24}$ -1.3° (c 3.13, $CHCl_3$).

pmr (CCl_4): τ 6.35 (s, 3H), 6.95 (t, J = 6, 1H), 8.3-8.8 (m, 2H), 8.55 (s, 3H), 9.0 (t, J = 6.5, 3H)

elemental analysis: calcd for $C_7H_{12}O_3$: C 58.32, H 8.39

found: C 58.39, H 8.45

glpc: UCW-98, 100°

(+)-2R,3S-Epoxy-2R-methylpentanal (103)

A solution of diisobutylaluminum hydride (2.01 g, 14.5 mM, 38% excess) in anhydrous ether (10 ml) was added dropwise over 40 min at -78° to a solution of ester 118 (1.51 g, 10.5 mM) in ether (10 ml). Stirring was continued for exactly 80 min from the beginning of the addition. Then aqueous saturated ammonium chloride (3 ml) was added to the reaction mixture at -78°, and the mixture allowed to warm to room temperature. Anhydrous sodium sulphate and Celite were added to the pasty mixture. The mixture was filtered with positive argon pressure and the filter pad washed with ether (30 ml). Three runs on this scale were combined. The ether was dried (Na_2SO_4) and carefully concentrated by distillation. The residue was molecularly distilled (oil bath 50°, 15 mm) to give 1.72 g (62%) of 103, $[\alpha]_D^{22}$ + 85° (c 2.82, $CHCl_3$). The material was too unstable to allow an accurate elemental analysis to be performed.

ir ($CHCl_3$): 2895, 2835, 1750 (s)

pmr ($CDCl_3$): τ 1.14 (s, 1H), 6.95 (t, J = 6, 1H), 8.4 (qu, J = 6, 2H), 8.7 (s, 3H), 8.95 (t, J = 6, 3H).

glpc: UCW-98, 85°

Hydrolysis of lactonic methyl ester 25

Aqueous 0.42N potassium hydroxide (1.55 ml, 0.65 mM) was added to a stirred solution of lactonic ester 25 (56 mg, 0.26 mM) in tert-butyl alcohol (2 ml) at 10°. After stirring at room temperature for 8 hr, the mixture was concentrated to approximately 1.5 ml, cooled to 0°, acidified to pH 1.5 with aqueous 2N hydrochloric acid, saturated with sodium chloride, and extracted with chloroform (2,3,3,1 ml).

The solvent was dried ($MgSO_4$) and evaporated to give 52 mg (100%) of chromatographically and spectroscopically pure 6 as white prisms. Recrystallization from ether-pentane afforded 50 mg (96%) of white needles (mp 119-120°). Neither epimerization nor elimination was observed during this hydrolysis.

All attempts to isolate methyl 7-potassium 3S-hydroxy-2R,4S,6R-trimethylheptan-1,7-dioate 119 by reacting 25 with 1.0 equivalent of potassium hydroxide were unsuccessful due to the facile lactonization back to 25.

5-Hydroxypentanoic 1,5-lactone (120) (δ-Valerolactone)

This reaction was carried out using the procedure reported by Smissman and coworkers.[159] Trifluoroacetic acid anhydride (25.5 ml, 180 mM) was added over 30 min to a stirred suspension of 90% hydrogen peroxide (4.1 ml, 150 mM) and anhydrous dichloromethane (25 ml) at 0°. After stirring for 15 min the peracid solution (0°) was added over 1 hr to a vigorously stirred suspension of disodium hydrogen phosphate (40 g, 280 mM) and cyclopentanone (8.4, 100 mM) in anhydrous dichloromethane (100 ml) at 0°. The reaction was stirred at 0° for 3 hr and then at room temperature for 18 hr. Water (100 ml) was added and the layers separated. The aqueous

phase was extracted with dichloromethane (50 ml) and the combined organic phase washed with aqueous saturated sodium bicarbonate (2 x 50 ml) and aqueous 10% sodium sulphite (50 ml). The organic layer was dried (Na_2SO_4) and evaporated to give a residue which was distilled to give 7.1 (71%) of 120 as a colourless liquid (bp 83°, 4 mm).
ir (CCl_4): 1735 (s)
pmr ($CDCl_3$): τ 5.55 (m,2H), 7.35 (m, 2H), 8.05 (m, 4H)

Triphenylmethylphosphonium Iodide

The reaction was carried out according to the procedure reported by Wittig and Schoellkopf.[160]

Iodomethane (8.2 g, 58 mM) was added in several portions to a solution of triphenylphosphine (11 g, 42 mM) in anhydrous benzene (50 ml). An immediate white precipitate formed upon addition of the iodide. After 48 hr at room temperature the white solid was collected by filtration, washed with warm (50°) benzene and dried (100°, 10 mm) to give 17 g (100%) of the phosphonium salt.
pmr ($CDCl_3$): τ 2.2 (cd, J = 7.0, 15H), 6.8 (d, J = 13.5, 3H)

Phosphorane Opening of δ-Valerolactone

Sodium hydride (50% dispersion in mineral oil, 192 mg, 4.0 mM) was added to anhydrous dimethylsulphoxide (4 ml), and the mixture heated at 70° for 45 min. A solution of triphenylmethylphosphonium iodide (1.62 g, 4.0 mM) in anhydrous dimethylsulphoxide (4 ml) was added to the cooled (25°) solution of methyl sulphinyl carbanion. After 10 min at room temperature, lactone 120 (200 mg, 2.0 mM) was added to the ylid solution. After 24 hr at 60° the orange solution was poured into cold (0-5°) aqueous saturated sodium bicarbonate (10 ml) and the aqueous solution extracted with dichloromethane (4 x 25 ml). The organic layer was dried (Na_2SO_4) and evaporated to give 700 mg (93%) of phosphorane 121 which was used directly in the next reaction.

ir ($CHCl_3$): 3350 (bs), 1540 (s)

1-Phenyl-3-oxo-hept-2(E)-en-7-ol (122)

A solution of the previously obtained phosphorane 121 (700 mg, 1.86 mM) and freshly distilled benzaldehyde (350 mg, 3.72 mM) in anhydrous benzene (10 ml) was maintained at 60° for 24 hr. The reaction mixture was cooled to room temperature and the solvent evaporated. The residue was chromatographed on silicic acid (25 g, chloroform) to give 115 mg (30%) of 122.

ir ($CHCl_3$): 3500, 1700, 1660

pmr ($CDCl_3$): τ 2.65 (m, 5H), 3.15 (d, J = 16, 1H),
3.65 (d, J = 16, 1H), 5.1 (t, J = 3.5, 1H),
5.9 (t, J = 5.5, 2H), 7.5-8.5 (m, 6H)

(±)-Methyl 7-Hydrogen 2,4*S*,6*R*-Trimethylhept-2(*E*)-en-1,7-dioate (**123**)

A methyl sulphinyl carbanion solution (0.16*M*, 1.25 ml, 0.20 mM) in dimethylsulphoxide was added to a stirred solution of triphenylmethylphosphonium iodide. After 10 min at room temperature, the resulting greenish yellow phosphorane solution was added over 5 min to a stirred solution of lactonic ester **25** (21.4 mg, 0.10 mM) in dimethylsulphoxide (1.0 ml). The colour of the phosphorane discharged during the addition until approximately half of the phosphorane had been added, then the mixture became yellow. After 20 hr at room temperature the reaction was added to cold (0-5°) aqueous 0.05*N* sodium bicarbonate (6 ml). The aqueous solution was extracted with chloroform (5 x 5 ml), cooled to 0°, acidified to pH 2 with aqueous 2*N* hydrochloric acid, and extracted with ether (5 x 5 ml). The combined ether layer was dried (Na_2SO_4) and evaporated to give 11 mg (50%) of the unsaturated half ester **123** as a colourless viscous liquid. The chloroform extract contained a mixture of triphenylmethylphosphonium iodide, diphenyl methylphosphine oxide, and the half ester in the approximate ratio of 2.5:2:1 as determined by pmr spectroscopy. ir ($CHCl_3$): 3500-2500 (bs), 1720 (s) pmr ($CDCl_3$): τ 1.65 (bs, 1H), 3.5 (dd, J = 10.3, 1.5, 1H), 6.25 (s, 3H), 7.5 (m, 2H), 8.15 (d, J = 1.5, 3H), 8.2-8.6 (m, 2H), 8.8 (d, J = 7, 3H), 8.95 (d, J = 6.5, 3H)

A series of experiments were carried out starting with lactonic methyl ester **25**, from which compounds **124**, and **126** through **131** were synthesized. The experimental details for these conversions are the same as those described below for the corresponding S-tert-butyl thioates **134**-**139**. The spectral details for the methylated compounds are given below.

(±)-Methyl 7-(tert-Butyldimethylsilyl) 3S-(tert-Butyldimethylsiloxy)-2R,4S,6R-trimethylheptan-1,7-dioate (**126**)

ir ($CHCl_3$): 1730, 1710

pmr ($CDCl_3$): τ 6.1 (dd, J = 7, 3, 1H), 6.35 (s, 3H), 7.4 (m, 2H), 8.0-8.6 (m, 3H), 8.6-9.0 (m, 9H), 9.06 (s, 9H), 9.12 (s, 9H) 9.75 (s, 6H), 9.94 (s, 6H)

(±)-Methyl 7-Hydrogen 3*S*-(*tert*-Butyldimethylsiloxy)-2*R*,4*S*,6*R*-trimethylheptan-1,7-dioate (**127**)

ir (CCl_4): 3400-2300 (bs), 1735 (s), 1705 (s)

pmr (CCl_4): τ -2.0 (bs, 1*H*), 6.15 (m, 1*H*), 6.32 (s, 3*H*), 7.4 (m, 2*H*), 8.0-8.5 (m, 3*H*), 8.6-9.0 (m, 9*H*), 9.05 (s, 9*H*), 9.9 (s, 6*H*)

Imidazolide **128**

ir (CCl_4): 3120 (w), 1735 (s), 850 (m)

pmr ($CDCl_3$): τ 1.75 (bs, 1*H*), 2.50 (bs, 1*H*), 2.85 (bs, 1*H*), 6.13 (m, 1*H*), 6.35 (s, 3*H*), 6.9 (m, 1*H*), 7.4 (m, 1*H*), 7.9-8.4 (m, 3*H*), 8.67 (d, J = 7, 3*H*), 8.86 (d, J = 7, 3*H*), 9.05 (d, J = 7.1, 3*H*), 9.1 (s, 9*H*), 9.95 (s, 6*H*)

Triphenylmethylene Phosphorane **124**

ir (CCl_4): 3060 (w), 1735 (s), 1535 (bs)

pmr (CCl_4): τ 2.2-2.7 (m, 15*H*), 6.15 (m, 1*H*), 6.3 (bd, 1*H*), 6.47 + 6.53 (s, 3*H*, *ca*. 1:1), 7.4 (m, 2*H*), 7.8-8.5 (m, 3*H*), 8.6-9.0 (m, 9*H*), 9.1 (s, 9*H*), 9.95 (bs, 6*H*)

Methyl 3*S*-(*tert*-Butyldimethylsiloxy)-10*S*,11*S*,-epoxy-7-oxo-2*R*,4*S*,6*R*,10*S*-tetramethyltridec-8(*E*)-enoate (**130**)*

ir (CCl_4): 1735 (s), 1690 (m), 1670 (m), 1625 (m), 845 (s)

pmr ($CDCl_3$): τ 3.32 (dd, J = 16, 1*H*), 3.64 (dd, J = 16, 1*H*), 6.15 (m, 1*H*), 6.35 (s, 3*H*), 7.0-7.5 (m, 3*H*), 8.1-8.5 (m, 5*H*), 8.55 (s, 3*H*), 8.65-9.0 (m, 12*H*), 9.1 (s, 9*H*), 9.95 (s, 3*H*), 9.98 (s, 3*H*)

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* With the attachment of the resolved aldehyde to the racemic right hand portion of the methynolide precursor, the subsequent compounds are no longer racemic. Instead a mixture of two compounds is present, until final resolution occurs during lactonization to methynolide (*vide infra*). The *R*, *S* notation used in the title compounds refers to the absolute configurations of the chiral centres of the correctly paired diastereoisomers of the left and right hand segments.

Methyl 3S-(tert-Butyldimethylsiloxy)-10S,11R-dihydroxy-7-oxo-2R,4S,6R,10S-tetramethyltridec-8(E)-enoate (131)

ir (CCl_4): 3470 (bs), 1730 (s), 1690 (m), 1675 (m)
1625 (m), 845 (s)

pmr ($CDCl_3$): 3.34 (dd, J = 16, 1H), 3.65 (dd, J = 16, 1H), 6.15 (m, 1H), 6.35 (s, 3H), 6.65 (bdd, J = 9.5, 2.5, 1H), 7.0-8.0 (m, 2H + 2 OH), 8.1-9.1 (md, 17H), 8.67 (s, 3H), 9.15 (s, 9H), 9.95 (s, 6H)

Thallium(I) 2-Methylpropane-2-thiolate

2-Methylpropane-2-thiol (1.98 g, 22 mM) was added dropwise over 5 min to a stirred solution of thallium(I) ethoxide (5.0 g, 20.0 mM) in anhydrous benzene (20 ml). After 15 min the precipitate was filtered under argon and washed with anhydrous pentane (3 x 10 ml) to give 5.6 g (95%) of thallium(I) 2-methylpropane-2-thiolate as bright yellow crystals (mp 170-175° decomp).

(±)-(*S*-*tert*-Butyl) 7-Hydrogen 3*S*-Hydroxy-2*R*,4*S*,6*R*-trimethylheptan-1-thioate-7-oate 3,7-lactone (**133**)

A suspension of lactonic acid **6** (1.00 g, 5.0 mM) and freshly distilled oxalyl chloride (1.28 g, 10.0 mM) in anhydrous benzene (30 ml) was stirred at room temperature for 18 hr. The resulting colourless solution was evaporated to give 1.10 g (100%) of lactonic acid chloride **132** as white needles.

ir ($CHCl_3$): 1790, 1735

Thallium(I) 2-methylpropane-2-thiolate (1.47 g, 5.0 mM) was added to a stirred solution of the above acid chloride (1.10 g, 5.0 mM) in anhydrous ether (30 ml) at 0°. The bright yellow colour of the thallium salt discharged almost immediately. The resulting milky suspension was stirred for 1 hr at room temperature, filtered through Celite and the filter pad washed with ether (4 x 20 ml). The combined filtrate was concentrated and the residue was flash distilled to give 1.36 g (100%) of **133** as a colourless viscous liquid (bp 110°, 0.2 mm).

ir ($CHCl_3$): 1735 (s), 1675 (s)

pmr ($CDCl_3$): τ 5.57 (dd, J = 9.5, 3.8, 1*H*), 7.36 (dq, J = 7.0, 3.8, 1*H*), 7.54 (bsept, 1*H*), 7.8-8.5 (m, 3*H*), 8.51 (s, 9*H*), 8.71 (d, J = 7.0, 3*H*), 8.76 (d, J = 7.0, 3*H*), 8.98 (d, J = 6.4, 3*H*)

(+)-(*S*-*tert*-Butyl) 7-(*tert*-Butyldimethylsilyl) 3*S*-(*tert*-Butyldimethylsiloxy)-2*R*,4*S*,6*R*-trimethylheptan-1-thioate-7-oate (**134**)

Aqueous 0.28*N* potassium hydroxide (13.7 ml, 3.84 mM, 0.92 equiv) was added dropwise at room temperature to a stirred solution of thiol ester **133** (1.14 g, 4.17 mM) in *tert*-butyl alcohol (10 ml) containing a trace of phenolphthalein at such a rate that the initially formed red colour faded away to colourless (or very pale pink); the addition took approximately 5 hr. After the addition was completed, the reaction mixture was stirred for 1 hr, and the solvent carefully removed at room temperature under reduced pressure (0.01 mm). The residue was dried by coevaporation with a mixture of anhydrous *N*,*N*-dimethylformamide and pyridine (1:1, 10 ml) at room temperature. The ring-opened potassium salt was thus obtained as a slightly hygroscopic white solid.

Imidazole (2.36 g, 34.6 mM, 9 equiv) was added to a stirred suspension of the above potassium salt (3.84 mM) in anhydrous *N*,*N*-dimethylformamide (20 ml). *tert*-Butyldimethylchlorosilane (2.30 g, 15.4 mM, 4 equiv) was then added to the resulting pale yellow solution and the reaction mixture maintained at 60° for 64 hr. The reaction was cooled to room temperature and the solvent was removed under reduced pressure (0.01 mm). The residue was diluted with ether (50 ml) and cold water (35 ml) containing a trace of bromocresol green. The mixture was cooled to 0° and acidified to pH 3.5, as indicated by the colour change from blue to yellow in the aqueous layer, by the dropwise addition of aqueous 2N hydrochloric acid. The two layers were separated and the aqueous phase was extracted with ether (3 x 20 ml). The combined ether layer was washed with aqueous saturated sodium chloride (20 ml) and the solvent evaporated. The residue was dissolved in dichloromethane (30 ml), dried (Na_2SO_4) and the solvent evaporated. The residual pale yellow liquid was flash distilled to give 1.97 g (96%) of disilyl compound 134 as a colourless liquid (bp 130°, 0.1 mm).

ir (CCl_4): 1715 (s), 1675 (s)

pmr ($CDCl_3$): τ 6.05 (dd, J = 6.2, 3.5, 1H), 7.1-7.8 (m, 2H), 8.0-8.4 (m, 3H), 8.5 (s, 9H), 8.6-9.0 (m, 9H), 9.05 (s, 9H), 9.1 (s, 9H), 9.7 (s, 6H), 9.9 (s, 6H)

(+)-(*S*-*tert*-Butyl) 7-Hydrogen 3*S*-(*tert*-Butyldimethylsiloxy)-2*R*,4*S*,6*R*-trimethylheptan-1-thioate-7-oate (**135**)

A solution of diester **134** (1.97 g, 3.68 mM) in *tert*-butyl alcohol (12.5 ml) was hydrolysed with aqueous 0.28*N* potassium hydroxide (12.5 ml, 3.50 mM, 0.95 equiv) according to the same procedure used for the lactone opening of **133**; the addition of the base took 45 min. The *tert*-butyl alcohol was evaporated and the remaining aqueous solution was diluted with ether (20 ml) and water (10 ml). The mixture was cooled to 0° and acidified against bromocresol green using aqueous 2*N* hydrochloric acid. The two layers were separated and the aqueous phase was extracted with ether (3 x 20 ml). Evaporation of the combined ether layers gave approximately 1.8 g of crude acid **135** as a pale yellow liquid. This material was chromatographed on silicic acid (100 g, chloroform) to give 1.40 g (94%) of chromatographically pure **135** as a colourless liquid.

ir ($CHCl_3$): 3500-2300 (bs), 1700 (s), 1675 (bs)

pmr ($CDCl_3$): τ 1.0 (bs, 1*H*), 6.05 (dd, J = 7.2, 2.8, 1*H*), 7.3 (bq, J ≃ 7, 1*H*), 7.2-7.7 (m, 1*H*), 8.0-8.4 (m, 3*H*), 8.45 (s, 9*H*), 8.85 (d, J = 7.0, 3*H*), 8.75 (d, J = 7.0, 3*H*), 8.75 (d, J = 6.8, 3*H*), 9.05 (s, 9*H*), 9.85 (s, 6*H*)

Imidazolide 136

According to the procedure of Staab and Bräunling[148a] N,N-carbonyldiimidazole (561 mg, 3.46 mM) was added to a stirred solution of acid 135 (1.40 g, 3.46 mM) in dichloromethane (10 ml). The reaction was stirred at room temperature for 3 hr and the solvent was then evaporated. The residue was triturated with cyclohexane (15, 10, 2 x 5 ml), and the combined solvent dried (Na_2SO_4) and evaporated to give 1.58 g (100%) of 136 as a pale yellow liquid.

ir ($CHCl_3$): 1735 (s), 1675 (s), 960 (s), 860 (s)

pmr ($CDCl_3$): τ 1.75 (bs, 1H), 2.50 (bs, 1H), 2.90 (bs, 1H), 6.1 (dd, J = 7.0, 2.5, 1H), 6.9 (m, 1H), 7.4 (m, 1H), 7.9-8.4 (m, 3H), 8.55 (s, 9H), 8.67 (d, J = 7.0, 3H), 8.85 (d, J = 7.0, 3H), 9.0 (d, J = 6.5, 3H), 9.1 (s, 9H), 9.95 + 9.98 (s, 6H).

Salt-free Triphenylmethylene Phosphorane

The reaction was carried out according to the procedure reported by Schlosser and Christmann.[145b] The triphenylmethylphosphonium bromide was prepared in the same way as the iodide described above.

Anhydrous ammonia (75 ml) was condensed into a flask at -78° and further dried by the addition of several small pieces of sodium metal. Approximately 60 ml of ammonia was then distilled from this intense blue solution into a second flask. A trace of iron(III) chloride was added to the liquid ammonia, followed by sodium metal (190 mg, 8.25 mg-atom). Finely powdered anhydrous triphenylmethylphosphonium bromide (2.46 g, 6.90 mM) was then added in small portions at such a rate that the blue colour of the ammonia changed to slightly brown. After the addition was complete, the reaction mixture was refluxed (-33°) for 30 min before the ammonia was allowed to slowly evaporate. The solid green-yellow residue was then dried at room temperature under reduced pressure (0.01 mm). This material was refluxed in anhydrous benzene (40 ml) for 10 min, cooled to room temperature, and filtered under argon to afford a bright yellow solution of the ylid. The concentration (0.17M) was determined by titration of the phosphorane with a standard solution of butanal in benzene. The Wittig reagent could be kept under argon at -15° for several months without appreciable decomposition.

Triphenylmethylene Phosphorane 137

The procedure of Staab *et al.*[145a] was used in this reaction.

A benzene solution (0.17M, 20.4 ml, 3.46 mM) of salt-free triphenylmethylene phosphorane was added to a stirred solution of imidazolide 136 (1.57 g, 3.46 mM) in anhydrous benzene (30 ml) at such a rate that the initially produced yellow colour of the phosphorane faded away to colourless; the addition took 30 min. The mixture was stirred at room temperature for 2 hr before the solvent was evaporated. The ice-cooled residue was diluted with ether (40 ml) and then aqueous saturated sodium bicarbonate (30 ml) was added. After stirring at 0° for 10 min, and then at room temperature for 5 min, the mixture was separated and the aqueous layer extracted with ether (3 x 25 ml). The combined ether layer was washed with aqueous saturated sodium chloride (20 ml), dried (Na_2SO_4) and evaporated. The residue was further dried by coevaporation with anhydrous benzene to give 2.25 g (98%) of 137 as a pale yellow liquid.

ir ($CHCl_3$): 1675 (s), 1535 (bbs), 960 (s), 850 (s)

pmr ($CDCl_3$): τ 2.2-2.7 (m, 15H), 6.1 (m, 1H), 6.28 (bd, 1H), 7.1-7.8 (m, 2H), 8.0-8.5 (m, 3H), 8.56 + 8.59 (s, 9H, *ca.* 3:1), 8.60-9.05 (m, 9H), 9.9 + 10.0 (s, 6H, 1:1)

S-*tert*-Butyl 3*S*-(*tert*-Butyldimethylsiloxy)-10*S*,11*S*-epoxy-7-oxo-2*R*,4*S*,6*R*,10*S*-tetramethyltridec-8(*E*)-enthioate (**138**)*

A solution of (±)-phosphorane **137** (2.25 g, 3.4 mM) and (+)-2*R*,3*S*-epoxy-2*R*-methylpentanal **103** (780 mg, 6.8 mM) in anhydrous toluene (20 ml) was stirred at 100° for 10 hr and then refluxed for 30 hr. The reaction was cooled to room temperature, the solvent evaporated and the residue triturated with anhydrous pentane (5 x 20 ml). Evaporation of the combined pentane extract gave an amber liquid which was chromatographed on silicic acid (100 g, carbon tetrachloride-chloroform) to give 880 mg (52%) of chromatographically pure **138**.

ir (CHCl$_3$): 1690 (s), 1675 (s), 1630 (m), 960 (s), 880 (m), 845 (s)

pmr (CDCl$_3$): τ 3.31 (d, J = 16, 1*H*), 3.62 + 3.65 (d, J = 16, 1*H*, *ca*. 5:4), 6.16 (dd, J = 6.8, 2.9, 1*H*), 7.1-7.5 (m, 3*H*), 8.1-8.6 (m, 5*H*), 8.55 (s, 12*H*), 8.7-9.0 (m, 12*H*), 9.1 (s, 9*H*), 9.9 (s, 6*H*).

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* See footnote on page 191.

S-tert-Butyl 3S-(tert-Butyldimethylsiloxy)-10S,11R-dihydroxy-7-oxo-2R,4S,6R,10S-tetramethyltridec-8(E)-enthioate (139)

Aqueous 2.1N sulphuric acid (1.67 ml, 3.5 mm) was added to a stirred solution of epoxide 138 (880 mg, 1.76 mM) in tetrahydrofuran (10 ml). The reaction was then stirred at room temperature for 44 hr, cooled to 0° and diluted with cyclohexane (30 ml) and water (30 ml). The mixture was carefully taken to pH 7 by the addition of solid sodium bicarbonate. After separation, the aqueous layer was extracted with cyclohexane (30, 25, 20, 15 ml). The combined organic layer was washed with aqueous saturated sodium chloride (15 ml), dried (Na_2SO_4) and evaporated to give approximately 1 g of a colourless liquid. This material was chromatographed on silicic acid (80 g, chloroform) to give 740 mg (81%) of chromatographically pure 139.

ir ($CHCl_3$): 3470 (bm), 1690 (sh), 1675 (s), 1630 (m), 960 (s), 850 (m).

pmr ($CDCl_3$): τ 3.12 + 3.14 (d, J = 16, 1H, ca. 5:4), 3.53 + 3.55 (d, J = 16, 1H, ca. 5:4), 6.17 (dd, J = 7.4, 2.8, 1H), 6.6 (bdd, J = 9.5, 2.5, 1H), 7.0-7.5 (m, 2H + OH), 7.5-7.9 (bs, OH), 8.1-8.6 (m, 5H), 8.45 (s, 9H), 8.6 (s, 3H), 8.6-9.0 (m, 12H), 9.0 (s, 9H), 9.85 (s, 6H).

Recrystallization of 3-Chloroperbenzoic Acid

An abbreviated procedure for this purification has been reported by Schwartz and Blumbergs.[161] A more detailed description of the conditions is given below.

A solution of commercial 3-chloroperbenzoic acid (85%, 10 g) in benzene-ether (1:1, 200 ml) was washed with phosphate buffer (pH 7, 3 x 25 ml). The organic layer was dried ($MgSO_4$) and evaporated. The residue was suspended in anhydrous dichloromethane (100 ml) and filtered to remove any undissolved material. The filtrate was diluted with pentane (100 ml) and stored at -10° for 18 hr. The precipitated peracid was collected by filtration. Iodometric titration showed that the white, electrostatic needles (mp 94-95°) were greater than 99% pure. The recrystallized peracid could be stored in a plastic bottle at -10° for several months without decomposition.

Cyclohexanecarbonyl Chloride

Oxalyl chloride (25.4 g, 200 mM) was added to a solution of cyclohexanecarboxylic acid (12.8 g, 100 mM) in anhydrous benzene (250 ml) at 5°. After 24 hr at room temperature the solvent was evaporated and the residue distilled to give 13.8 g (94%) of a colourless liquid (bp 70°, 20 mm).

S-tert-Butyl Cyclohexanemethanethioate (140)

Thallium(I) 2-methylpropane-2-thiolate (2.94 g, 10.0 mM) was added to a solution of cyclohexanecarbonyl chloride (1.46 g, 10.0 mM) in anhydrous ether (50 ml) at 0°. The resulting milky suspension was stirred at room temperature for 1 hr and then filtered through Celite. The filter pad was washed thoroughly with ether (4 x 25 ml) and the combined ether solution evaporated . The residue was distilled to give 2.0 g (100%) of 140 (bp 88°, 2 mm). ir (CCl_4): 1675 (s)

Cyclohexylmethyl Cyclohexanecarboxylate (141, R = c-C_6H_{11}-CH_2OH)

Oxidative Activation:

Recrystallized 3-chloroperbenzoic acid (518 mg, 3.0 mM) was added to a solution of thiol ester 140 (200 mg, 1.0 mM) and cyclohexylmethanol (342 mg, 3.0 mM) in anhydrous dichloromethane (10 ml) at -78°. The reaction was stirred at this temperature for 1 hr and then allowed to warm to room temperature over 2 hr. The reaction mixture was diluted with dichloromethane (10 ml) and washed with aqueous saturated sodium bicarbonate (5 ml), dried ($MgSO_4$) and the solvent evaporated. The residue was purified by ptlc to give 173 mg (83%) of 141.

The properties of this material were identical with those of authentic material prepared from cyclohexanecarbonyl chloride and cyclohexylmethanol.

ir (CCl_4): 1730 (s)

The cyclohexanecarboxylates of methanol (100%), cyclohexanol (95%), 2,4-dimethylpentan-1-ol (75%), and 5,6-dihydroxy-5-methyl-3(*E*)-en-2-one (40%) were prepared in a similar manner.

The *S*-*tert*-butyl thioate may also be converted into the corresponding carboxylic acid by a modification of this esterification reaction. The carboxylic acid can be isolated (80-90%) from a 0.1*M* tetrahydrofuran solution of the thiol ester, 3-chloroperbenzoic acid and water in the ratio of 1:3:3, after overnight stirring at room temperature.

3*S*-(*tert*-Butyldimethylsiloxy)-10*S*,11*R*-dihydroxy-7-oxo-2*R*,4*S*,6*R*,10*S*-tetramethyltridec-8(*E*)-enoic acid (145)

Recrystallized 3-chloroperbenzoic acid (78 mg, 0.45 mM) was added to a stirred suspension of thiol ester 139 (60 mg, 0.135 mM), water (0.010 ml, 0.54 mM) and sodium benzoate (20 mg, 0.135 mM) in anhydrous tetrahydrofuran (3 ml) at 0°. The reaction was stirred at 0° for 30 min and then at room temperature for 12 hr. The mixture was diluted with ether (10 ml), cooled to 0°, and aqueous 0.3*M* sodium chloride-hydrochloric acid (pH 3.8, 7 ml) was added. The two phase mixture was then carefully taken to pH 3 at 0° (against bromocresol green) with aqueous 2*N* sulphuric acid, stirred at 0°

for 5 min and then separated. The aqueous layer was extracted with ether (10, 5, 5 ml), and the combined organic layer was washed with aqueous saturated sodium chloride (10 ml), dried ($MgSO_4$) and evaporated to give a white solid. Sublimation (40°, 0.1 mm) removed the crystalline benzoic acid. The pale yellow liquid residue was suspended in cold (0°) aqueous 0.25*N* sodium bicarbonate, and washed with dichloromethane (3 x 2 ml). The tlc and ir of the dichloromethane layer indicated the presence of unreacted starting thiol ester as a major component and a small amount of unidentified by-products which included anhydrides. Evaporation of the solvent left 35 mg of yellow liquid. The aqueous layer was acidified to pH 3 with aqueous 2*N* sulphuric acid and extracted with dichloromethane (3 x 5 ml). The combined organic phase was dried ($MgSO_4$) and evaporated to give a pale yellow tar. This material was purified by ptlc (silica gel, 2% ethanol-chloroform) to afford 20 mg (39%) of **145**.

ir ($CHCl_3$): 3400-2500 (bm), 1700 (s), 1630 (m), 745 (s)

pmr ($CDCl_3$): τ 1.4 (bs, 1*H*), 3.18 (cd, J = 16, 1*H*), 3.58 (cd, J = 16, 1*H*), 5.1 (m, 2 O*H*), 6.23 (bdd, J = 7, 4, 1*H*), 6.6 (bd, J = 10, 1*H*), 7.0-7.6 (m, 2*H*), 8.0-8.6 (m, 5*H*), 8.69 (s, 3*H*), 8.6-9.0 (m, 12*H*), 9.1 (s, 9*H*), 9.95 (s, 6*H*)

Natural Methynolide (14)

A suspension of methymycin (150 mg, 0.32 mM) in aqueous 5N sulphuric acid (7.5 ml) was stirred at room temperature for 20 sec and then refluxed for 5 min. The mixture darkened slightly and a precipitate appeared. The reaction mixture was immediately cooled, diluted with water (10 ml), and extracted with chloroform (20 ml, 3 x 10 ml). The organic phase was washed with water (3 x 5 ml), aqueous saturated sodium chloride (5 ml) and dried (Na_2SO_4). Evaporation of the solvent gave 105 mg of an oily residue which was chromatographed on silica gel (10 g). The eluent was initially carbon tetrachloride, but was gradually changed to chloroform. The methynolide eluted from the column using chloroform to give 61 mg (61%) of 14 (mp 158-160°, recrystallized from ether), $[\alpha]_D^{25}$ + 63° (methanol).

ir ($CHCl_3$): 3400 (bm), 1725 (s), 1685 (m), 1630 (m)

pmr ($CDCl_3$): τ 3.44 (d, J = 16.0, H-8), 3.74 (d, J = 16.0, H-9), 5.32 (dd, J = 10.3, 2.0, H-11), 6.53 (bd, J = 10.0, H-3), 6.83 (bs, OH-10), 7.46 (dq, J = 10.0, 7.0, H-2), 7.60 (m, H-6), 8.16 (m, 2H-12), 8.2-8.7 (m, 2H-5 + H-4), 8.72 (s, Me-10), 8.76 (d, J = 7.0, Me-2), 8.84 (d, J = 7.0, Me-6), 9.08 (d, J = 6.0, Me-4), 9.18 (t, J = 7.0, 3H-13).

uv (ethanol): λ_{max} 225 nm (log ε 4.03)

mass spectrum: 295 (P-17), 254 (P-58)

CD (c 0.008M, dioxane), 25°: $[\theta]_{237}$ -24860, $[\theta]_{295}$ + 203,
$[\theta]_{338}$ - 516

Synthetic methynolide from seco-acid 145

A benzene solution (0.05M, 0.80 ml, 0.040 mM) of freshly distilled trifluoroacetic acid anhydride was added to a stirred solution of seco-acid 145 (12 mg, 0.027 mM) in anhydrous benzene (2 ml) at 5°. The mixture was stirred at this temperature for 18 hr, at room temperature for 7 hr, and at 40° for 10 hr, before being diluted with anhydrous toluene (10 ml). The solvent was evaporated and the residue chromatographed on silicic acid (1.0 g, chloroform) to give a fraction (5.5 mg) which consisted mainly of the desired lactone and some uncyclized acid (the "wrong" isomer). This mixture was suspended in aqueous 0.25N sodium bicarbonate at 0°, and extracted with dichloromethane (3 x 1 ml). The combined organic layer was re-extracted with aqueous 0.25N sodium bicarbonate (1 ml), dried ($MgSO_4$) and evaporated. Recrystallization of the residue from ether-hexane gave 1.5 mg (19% based on the "right" isomer) of methynolide as white prisms (mp 159-161°). This material was identical in all respects with methynolide obtained from naturally occurring methymycin. Most of the CD absorption (95%) of the synthetic material at the specified wavelengths is due to methynolide.

mass spectrum: calcd for $C_{17}H_{27}O_4$ (P-17): $\underline{m}/\underline{e}$ = 295.1909

measured: $\underline{m}/\underline{e}$ = 295.1912

CD ($\underline{c}$ 0.006$\underline{M}$, dioxane), 25°: $[\theta]_{237}$ - 23600, $[\theta]_{295}$ + 193, $[\theta]_{338}$ - 490

Mercury(II) Trifluoroacetate

A mixture of mercury(II) oxide (108.3 g, 500 mM) and freshly distilled trifluoroacetic acid (137.0 g, 1.2 M) was heated at 80° for 30 min. The excess trifluoroacetic acid and the water formed in the reaction were removed from the solution under reduced pressure. The white crystalline residue was then dried (50°, 0.01 mm) for 48 hr to give a quantitative yield of product.

Cyclohexylmethyl Cyclohexanecarboxylate (141, R = $\underline{c}$-C_6H_{11}-CH_2OH)

Mercury(II) Activation:

Mercury(II) trifluoroacetate (85.5 mg, 2.0 mM) was added to a solution of thiol ester 140 (200 mg, 1.0 mM) and cyclohexylmethanol (228 mg, 2.0 mM) in anhydrous acetonitrile (10 ml). After 30 min at room temperature the reaction mixture was filtered to remove insoluble mercury compounds. The filter pad was washed with ether (2 x 10 ml) and the combined organic phase washed with aqueous saturated sodium bicarbonate (5 ml), aqueous saturated sodium chloride (5 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue purified by ptlc to give 183 mg (88%) of pure 141.

Other esters prepared using this method are summarized in Table 9 of the text.

O,O-Dimethylzearalenone

Finely powdered potassium carbonate (3.38 g, 20 mM) and dimethylsulphate (1.546 g, 10 mM) were added to a solution of zearalenone (390 mg, 1.228 mM) in anhydrous acetone (40 ml). The reaction mixture was refluxed for 18 hr, cooled to room temperature, and the solids removed by filtration through Celite. The filter pad was washed with acetone (3 x 10 ml) and the combined filtrate evaporated. The solid residue was recrystallized from ether to give 407 mg (96%) of pure material (mp 115-116°).

ir ($CHCl_3$): 1710 (s), 1600 (s), 1575 (m)

pmr ($CDCl_3$): τ 3.4 (d, J = 3, 1H), 3.6 (bd, J = 16, 1H), 3.65 (d, J = 3, 1H), 3.95 (m, 1H), 4.7 (m, 1H), 6.18 (s, 3H), 6.21 (s, 3H), 7.1-8.5 (m, 12H), 8.65 (d, J = 7, 3H)

O,O-Dimethylzearalenone Ethylene Ketal (148)

This reaction and the one following were carried out using the method described by Taub *et al*.[105a]

A solution of dimethylzearalenone (407 mg, 1.18 mM) in anhydrous benzene (8.5 ml) was treated with ethylene glycol (825 mg, 10 mM), trimethoxyorthoformate (705 mg, 5 mM) and 4-toluenesulphonic acid (25 mg). The reaction mixture was heated at 60° for 5 hr, cooled to room temperature and poured into a mixture of aqueous saturated sodium bicarbonate (5 ml) and aqueous saturated sodium chloride (5 ml). The mixture was extracted with ether (3 x 50 ml). The organic phase was washed with pH 7 buffer (25 ml), dried ($MgSO_4$) and evaporated. The resulting oil solidified on standing. Recrystallization of this material from ether gave 423 (92%) of pure ketal 148 (mp 104-105°).

ir ($CHCl_3$): 1710 (s), 1600 (s), 1575 (m)

pmr ($CDCl_3$): τ 3.42 (d, J = 3, 1H), 3.6-3.9 (m, 3H), 4.8 (m, 1H), 6.1 (s, 4H), 6.21 (s, 3H), 6.28 (s, 3H), 7.7-8.7 (m, 12H), 8.68 (d, J = 7, 3H)

O,O-Dimethylzearalenone Seco-acid Ethylene Ketal (146)

A solution of ketal 148 (262 mg, 0.672 mM) in anhydrous dimethylsulphoxide (3.15 ml) was treated dropwise at room temperature with aqueous 6N sodium hydroxide (2.0 ml). After 6 hr at 120° the reaction mixture was cooled to room temperature and poured into aqueous saturated sodium chloride (10 ml). The mixture was extracted with carbon tetrachloride (3 x 75 ml). The aqueous layer was separated, mixed with ether (10 ml) and carefully acidified against bromocresol green at 0°. The aqueous layer was extracted with ether (3 x 50 ml) and the combined ether layer was dried ($MgSO_4$) and evaporated. The residue was coevaporated with anhydrous benzene (2 x 10 ml) and finally dried under reduced pressure (0.01 mm) to give 273 mg (98%) of seco-acid 146.

ir ($CHCl_3$): 3500 (bw), 1715 (bs), 1590 (s), 1570 (m)

pmr ($CDCl_3$): τ 3.25 (d, J = 16, 1H), 3.42 (d, J = 3, 1H), 3.72 (d, J = 3, 1H), 3.90 (d, J = 16, 1H), 4.3 (bs, 2H, [OH]), 6.10 (s, 4H), 6.18 (s, 3H), 6.21 (s, 3H), 6.2-6.4 (m, 1H), 7.7-8.0 (m, 3H), 8.0-8.65 (m, 9H), 8.82 (d, J = 7, 3H)

S-*tert*-Butyl Thioate of *O*,*O*-Dimethylzearalenone Seco-acid Ethylene Ketal (147)

Diethyl phosphorochloridate (86.3 mg, 0.5 mM) dissolved in anhydrous tetrahydrofuran (1 ml) was added dropwise at 0° over 10 min to a stirred solution of seco-acid 146 (204 mg, 0.5 mM) and triethylamine (50.6 mg, 0.5 mM) in anhydrous tetrahydrofuran (4 ml). After 3 hr at room temperature the reaction mixture was filtered through Celite to remove the precipitated triethylamine hydrochloride. The filter pad was washed with anhydrous tetrahydrofuran (2 x 5 ml) and the combined filtrate treated with thallium(I) 2-methylpropane-2-thiolate (162 mg, 0.55 mM). After 18 hr at room temperature the milky white mixture was filtered through Celite. The filter pad was washed with tetrahydrofuran (10 ml) and the combined filtrate evaporated. The residue was dissolved in ether (25 ml), washed with water (25 ml) and aqueous saturated sodium chloride (2 x 5 ml), and dried ($MgSO_4$). Evaporation of the solvent gave 237 mg (98%) of chromatographically pure 147.

ir ($CHCl_3$): 3620 (w), 1665 (s), 1600 (s), 1575 (m)

pmr ($CDCl_3$): τ 3.35 (d, J = 3, 1H), 3.6-4.05 (m, 3H), 6.1 (s, 4H), 6.2 (s, 3H), 6.25 (s, 3H), 6.2-6.4 (m, 1H), 7.7 (bq, J = 8, 2H), 8.2 (bs, OH), 8.45 (s, 9H), 8.0-8.7 (m, 10H), 8.85 (d, J = 7, 3H) mass spectrum: 480 (P)

Cyclization of 147: Mercury(II) Activation

Ketal thiol ester 147 (100 mg, 0.21 mM) was cyclized in 90% isolated yield to O,O-dimethylzearalenone ethylene ketal using the same procedure given above for cyclohexylmethyl cyclohexanecarboxylate. The material was identical in all respects to authentic material.

3-(tert-Butyldimethylsiloxy)methynolide (natural) (149)

tert-Butyldimethylchlorosilane (13.3 mg, 0.088 mM, 1.25 equiv) was added to a solution of imidazole (12.4 mg, 0.18 mM, 2.5 equiv) and naturally derived methynolide (23.0 mg, 0.074 mM) in anhydrous N,N-dimethylformamide (0.50 ml). The solution was maintained at 60° for 64 hr, cooled to room temperature and the solvent removed under reduced pressure (0.01 mm). The residue was dissolved in dichloromethane (10 ml), washed with water (2 x 1 ml) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by ptlc (silica gel, ethyl acetate-hexane 1:2) to give 4.7 mg (15%) of 149.

ir ($CHCl_3$): 3400 (bm), 1725 (s), 1690 (m), 1630 (m), 850 (m) pmr ($CDCl_3$): τ 3.44 (d, J = 16.0, H-8), 3.69 (d, J = 16.0, H-9), 5.28 (dd, J = 10.0, 2.5, H-11), 6.38 (bt, J ≈ 5, H-3), 6.43 (bs, OH-10), 7.25-7.7 (m, H-2, H-6), 7.7-8.5 (m, H-4, 2H-5, 2H-12), 8.64 (s, Me-10), 8.77 (d, J = 7, Me-2), 8.83 (d, J = 7, Me-6), ~9.1 (d, J = 6, Me-4), ~9.1 (t, J = 7, 3H-13), 9.11 (s, *tert*-BuSiO-3), 9.95 (s, 2 MeSiO-3)

3-(*tert*-Butyldimethylsiloxy)methynolide (synthetic) (**149**)

Mercury(II) trifluoroacetate (86 mg, 0.20 mM) was added to a solution of thiol ester **139** (50.6 mg, 0.108 mM) in anhydrous acetonitrile (10 ml). After 2 hr at room temperature the solvent was evaporated and the residue suspended in ether (15 ml) and filtered to remove the insoluble mercury compounds. The filter pad was washed with ether (2 x 10 ml) and the combined ether layer washed with aqueous saturated sodium bicarbonate (2 x 5 ml) and aqueous saturated sodium chloride (2 x 5 ml). The aqueous layer was then back extracted with ether (2 x 25 ml) and the combined ether phase dried ($MgSO_4$) and evaporated to give 46 mg of crude material. A sample was purified by ptlc (silica gel, ethyl acetate-hexane 1:2).

The pmr spectrum of this material was identical to that of the naturally derived silyated methynolide. The crude product was used directly in the next reaction.

Tetrabutylammonium fluoride

The reaction was carried out according to the procedure reported by Corey and Venkateswarlu.[147]

Aqueous 10% tetrabutylammonium hydroxide (23.4 ml, 10 mM) was neutralized with 48% hydrofluoric acid (*ca*. 0.275 ml) at 0°. The solvent was removed under reduced pressure (0.01 mm), and the residue dried by coevaporation with benzene-acetonitrile (1:1, 2 x 50 ml) followed by final drying under reduced pressure (0.01 mm) for 24 hr at 35°.

Synthetic methynolide (from hydrolysis of silyl derivative **149**)

A tetrahydrofuran solution (0.3*M*, 0.860 ml, 0.26 mM) of tetrabutylammonium fluoride was added to a solution of the previously obtained siloxymethynolide **149** (46 mg, 0.108 mM) in anhydrous tetrahydrofuran (5 ml). After 30 hr at room temperature the solvent was removed and the residue purified by ptlc (silica gel, ethyl acetate-hexane 1:2) to give 10.1 mg (30%) of synthetic methynolide. Recrystallization from ether-hexane gave 9.2 mg of white crystals (mp 158-160°). This material was identical to the naturally derived methynolide in all respects.

1-β,2-Diacetoxydesosamine Hydrochloride (153)

Desosamine was obtained by degradation of erythromycin according to the method reported by Flynn and coworkers.[6]

Acetic anhydride (2.0 ml) was added to a suspension of desosamine hydrochloride (564 mg, 2.67 mM) in anhydrous pyridine (2.0 ml) at 0°. The resulting solution was stirred at room temperature for 18 hr, the solvent removed under reduced pressure (0.01 mm), and the residue triturated with chloroform-ethyl acetate (1:1, 10 ml). The resulting precipitate was collected by filtration and dried at room temperature under vacuum (0.01 mm) to give 615 mg (78%) of fine white crystals (mp 194-195.5°, decomp), $[\alpha]_D^{23}$ + 4.8° (c 1.0, H_2O).

pmr ($CDCl_3$): τ 4.32 (d, J = 7, 1H), 4.88 (dd, J = 10.5, 7, 1H), 5.7-6.2 (m, 2H), 7.15 (bs, 6H), 7.69 (s, 3H), 7.92 (s, 3H), 8.1-8.6 (m, 2H), 8.65 (d, J = 6, 3H).

1-α-Bromo-2-acetoxydesosamine Hydrobromide (154)

Acetic anhydride (0.050 ml) was added to a solution of diacetoxydesosamine hydrochloride 153 (23.7 mg, 0.08 mM) in a 30% acetic acid solution of hydrogen bromide (0.20 ml, 0.98 mM). After 1 hr at room temperature the solvent was removed under reduced pressure (0.01 mm). The residue was coevaporated with chloroform (2 x 5 ml) to give 28.9 mg (100%) of crude crystalline 154 (mp 159-168°, decomp), $[\alpha]_D^{23}$ + 207° (c 1.1, $CHCl_3$) which was sufficiently pure for use in further reactions.

pmr ($CDCl_3$): τ 3.3 (d, J = 4, 1H), 5.0 (dd, J = 11, 4, 1H), 5.3-6.3 (m, 2H), 7.0-8.3 (bm, 6H), 7.69 (s, 3H), 8.0-8.6 (m, 2H), 8.65 (d, J = 6, 3H)

1-β-Cholesteryl-2-acetoxydesosamine Hydrobromide (155)

Cholesterol (52.4 mg, 0.136 mM) and freshly prepared bromodesosamine 154 (147 mg, 0.41 mM) were dissolved in an anhydrous solution of chloroform and lutidine (1:1, 2.0 ml). After 18 hr at 50° the solvent was removed under reduced pressure (0.01 mm) and the residue chromatographed on silica gel (3 g, chloroform-methanol 40:1) to give 65.3 mg (72%) of 155 (mp 252-254°, decomp).

pmr ($CDCl_3$) - isolated peaks: τ 4.66 (d, J = 6.5, 1H), 5.05 (dd, J = 10, 6.5, 1H), 5.5 (d, J = 7, 1H), 6.1-6.7 (m, 2H), 7.19 (s, 6H), 7.74 (s, 3H).

elemental analysis: calcd for $C_{37}H_{65}O_4NBr$: C, 66.55, H, 9.81 N, 2.10

found: C, 66.49, H, 9.50 N, 2.29

1-α and 1-β-(2,4-Dimethylpentan-3-yl)-2-acetoxydesosamine Hydrobromide (156)

A mixture of α- and β-glycosides (67% yield) was obtained starting with 2,4-dimethylpentan-3-ol (53 mg, 0.50 mM) using the conditions given above for cholesterol.

The pmr spectrum of the product was complicated, but a doublet at τ 4.36, $J = 5$ Hz was assigned to the anomeric proton of the α-glycoside, and a doublet at τ 5.70, $J = 8$ Hz to the β-anomer. Integration of the spectrum indicated that the product consisted of an approximately equal mixture of the two anomers.

2'-Acetoxymethymycin (natural)

Acetic anhydride (0.20 ml) was added to a solution of naturally derived methymycin (17.8 mg, 0.038 mM) in anhydrous pyridine (0.30 ml) at 0°. After 18 hr at room temperature the solvent was removed under reduced pressure (0.01 mm). The residue was purified by ptlc (silica gel, chloroform-methanol 9:1) to give 8.9 mg (46%) of 2'-acetoxymethymycin and 5.4 mg (26%) of the known 2',10-diacetoxymethymycin.

2'-Acetoxymethymycin Hydrobromide (natural) (**157**)

A chloroform solution (0.01*N*, 2.45 ml, 0.0245 mM, 0.9 equiv) of hydrogen bromide was added dropwise over 7 min to a solution of 2'-acetoxymethymycin (14 mg, 0.0273 mM) in chloroform (0.50 ml). After 3 additional min of stirring the solvent was evaporated to give 17 mg of crude material. Purification by ptlc, using the same system as above for the free amine, yielded 15 mg (100%) of pure hydrobromide.

pmr ($CDCl_3$): τ 3.41 (d, J = 16, *H*-8), 3.70 (d, J = 16, *H*-9), 5.2 (t, J = 7, *H*-2'), 5.27 (dd, J = 11, 2, *H*-11), 5.7 (d, J = 7, *H*-1'), 6.3-6.7 (m, 2*H*), 7.2-7.6 (m, 4*H*), 7.45 (s, $N[CH_3]_2$), 7.93 (s, $C\underline{H}_3CO$), 8.91-9.0 (md, 22*H*), 8.65 (s, Me-10), 9.1 (t, J = 7, 3*H*-13).

2'-Acetoxymethymycin Hydrobromide (synthetic) (**157**)

A solution of synthetic methynolide (13.1 mg, 0.0419 mM) in anhydrous chloroform (0.20 ml) and lutidine (0.50 ml) was added to a solution of freshly prepared bromodesosamine **154** (73.2 mg, 0.20 mM) in chloroform (0.30 ml). Af[illegible] 18 hr at 50° the solvent was removed under reduced pressure (0.01 mm). The residue was purified by the same method as the natural material to give 10.7 mg (50%) of 157 as a colourless oil. The ir spectrum of this product was superimposable upon that of the naturally derived 2'-acetoxymethymycin hydrobromide except for a small peak at 1012 cm^{-1} attributable to the α-glycoside. The pmr spectrum of the product showed that approximately half of the material was the desired β-glycoside. There was 15-20% of the α-glycoside, and the remainder was unknown material. No attempt was made to separate the anomeric mixture at this stage.

Methymycin and *epi*-Methymycin (synthetic)

The previously obtained mixture of α- and β-2'-acetoxymethymycin hydrobromides (10.7 mg, 0.021 mM) was dissolved in a mixture of methanol, water and triethylamine (40:10:1, 0.5 ml). After 4,5 hr at room temperature the solvent was removed under reduced pressure (0.01 mm) to give 10.2 mg of colourless oil. Purification by ptlc (silica gel, chloroform-methanol 8:2) yielded 5.0 mg (25% based on methynolide) of methymycin and 1.3 mg of oily *epi*-methymycin. Recrystallization of the synthetic methymycin (β-glycoside), which has the natural configuration, from ethyl acetate gave 4.7 mg of fine white needles (mp 193-196°, decomp), $[\alpha]_D^{23}$ + 66.0° (*c* 0.40, $CHCl_3$).

ir ($CHCl_3$): 3450 (bm), 1730 (s), 1695 (s), 1635 (s)

pmr ($CDCl_3$): τ 3.5 (d, J = 16.0, H-8), 3.7 (d, J = 16.0, H-9), 5.25 (dd, J = 10.0, 2.5, H-11), 5.75 (d, J = 7.5, H-1'), 6.4 (bd, J = 10, H-3), 6.4-6.7 (bs, 2 OH), 6.8 (dd, J = 10.0, 7.5, H-2'), 7.0-7.8 (m, H-2, H-6, H-3', H-5'), 7.72 (s, $N[CH_3]_2$), 8.0-9.2 (m, 7H), 8.55 (d, J = 7, Me-5'), 8.62 (s, Me-10), 8.75 (d, J = 7, Me-2), 8.82 (d, J = 7, Me-6), 8.95 (d, J = 6, Me-4), 9.1 (t, J = 7, 3H-13)

epi-methymycin (α-glycoside)

pmr ($CDCl_3$): τ 3.4 (d, J = 16, H-8), 3.7 (d, J = 16, H-9), 4.92 (d, J = 4, H-1'), 5.25 (dd, J = 10, 2, H-11), 6.15 (bs, OH), 6.35 (d, J = 10, H-3), 6.5 (asym.q, H-2'), 7.0-7.8 (m, 4H), 7.7 (s, $N[CH_3]_2$), 8.1-8.6 (m, 7H), 8.6-9.0 (md, 15H), 9.1 (t, J = 7, 3H-13)

PART II

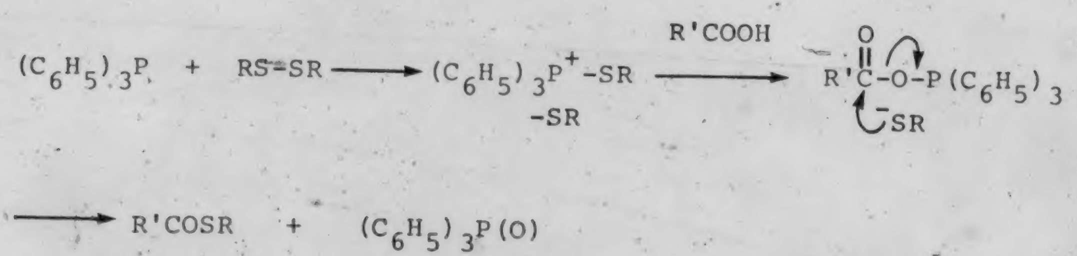
NEW REAGENTS FOR ORGANIC SYNTHESIS

CHAPTER 1

A GENERAL SELECTIVE SYNTHESIS OF THIOL ESTERS

During our synthetic study of the macrolide antibiotic methymycin, it became necessary to employ a protecting group for a carboxylic acid which was relatively stable to both acid and base, and which could be easily removed. For several reasons, we decided that the thiol ester function might serve this purpose. To our surprise, however, in spite of the ever increasing interest in the enzymatic synthesis of acyl-CoA[162a] and its involvement in fatty acid biosynthesis (acyl transfer reaction),[162b] there has never been developed a general, selective method to prepare thiol esters from carboxylic acids and thiols which is applicable to sensitive, complex organic substrates.[151a]

There were two recently reported procedures which were useful in certain cases, but both methods seem to be limited in scope. The procedure reported by Mukaiyama *et al*. in which a carboxylic acid is reacted with a disulphide and triphenylphosphine,[105d, 107c,d, 110] is applicable to the preparation of pyridine-2-thiol and benzenethiol esters, but not to that of alkanethiol esters. A possible mechanism for this reaction is given in the following scheme.

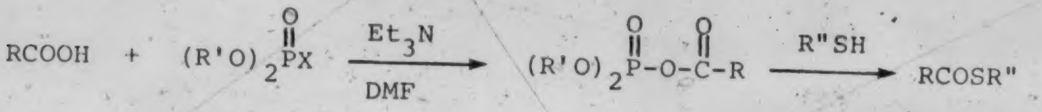


$$(C_6H_5)_3P + RS{-}SR \longrightarrow (C_6H_5)_3\overset{+}{P}{-}SR \;\; {-SR} \xrightarrow{R'COOH} R'\overset{O}{\overset{\|}{C}}{-}O{-}P(C_6H_5)_3 \;\; {SR}$$

$$\longrightarrow R'COSR + (C_6H_5)_3P(O)$$

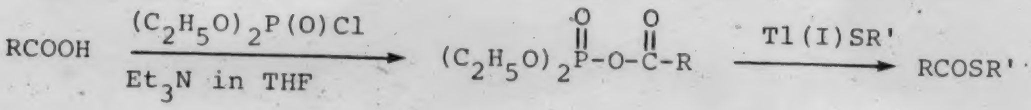
R = pyridine-2-thiol, benzenethiol

The other method, reported by Yamada et al.,[163] involves the reaction of diphenylphosphoryl azide or diethylphosphoryl cyanide with a carboxylic acid and a thiol to produce the corresponding thiol ester. This reaction unfortunately proceeds well only with less substituted (mainly primary) alkanethiols. The reaction probably follows the pathway given below.



$$RCOOH + (R'O)_2\overset{O}{\overset{\|}{P}}X \xrightarrow[DMF]{Et_3N} (R'O)_2\overset{O}{\overset{\|}{P}}{-}O{-}\overset{O}{\overset{\|}{C}}{-}R \xrightarrow{R''SH} RCOSR''$$

We were able to easily eliminate the remote possibility that $(C_2H_5O)_2P(O)SC_2H_5$ is an intermediate in Yamada's synthesis since no reaction occurred between this compound and cyclohexanecarboxylic acid in N,N-dimethylformamide even in the presence of triethylamine. If we accept the mechanism described above, it is obvious how we have to modify the reaction conditions in order to improve the efficiency and yield of the procedure. Firstly, a more effective and selective synthesis of carboxylic phosphoric anhydrides is required, and secondly we need to provide a stronger driving force in the second step in order to bring the reaction to completion. The reaction sequence that we found to be most satisfactory is formulated below.

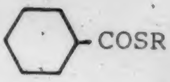
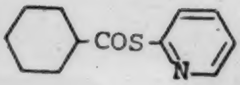
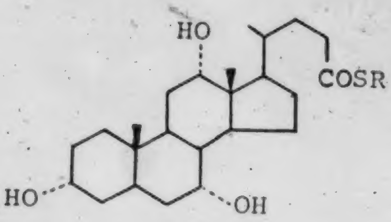
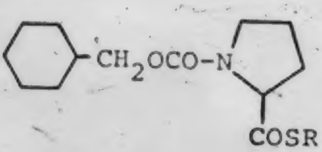


$$\mathrm{RCOOH} \xrightarrow[\mathrm{Et_3N\ in\ THF}]{\mathrm{(C_2H_5O)_2P(O)Cl}} \mathrm{(C_2H_5O)_2}\overset{O}{\overset{\|}{\mathrm{P}}}\text{-O-}\overset{O}{\overset{\|}{\mathrm{C}}}\text{-R} \xrightarrow{\mathrm{Tl(I)SR'}} \mathrm{RCOSR'}$$

We chose diethyl phosphorochloridate[164] because of its high selectivity towards the carboxy group with respect to hydroxy, a requirement that must be met in many cases. Both cyclohexanol and tert-butyl alcohol were recovered virtually quantitatively when allowed to react with the chloridate. The selectivity of this reagent, which is clearly demonstated by entries 3 and 4 of Table 10, can be favourably compared with that occurring with the methods involving triphenylphosphine and carbon tetrachloride (or conventional halogenating agents) which react with both the carboxy[165] and hydroxy groups.[166]

The triethylamine hydrochloride produced in the first step of the reaction quantitatively precipitates from the tetrahydrofuran solution and is removed by filtration. This ensures the complete formation of the

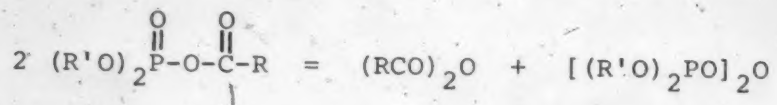
Table 10: Examples of the Thiol Ester Synthesis

Entry	Product		Yield (%)
1		R = $C(CH_3)_3$	94
		R = $CH(CH_3)_2$	90
		R = $(CH_2)_2CH_3$	91
		R = C_6H_5	92
2			90
3		R = $C(CH_3)_3$	86
		R = $CH(CH_3)_2$	90
		R = $(CH_2)_2CH_3$	86
4	$CH_3(CH_2)_5CH(OH)(CH_2)_{10}COSC(CH_3)_3$		84
5		R = $C(CH_3)_3$	89
		R = $CH(CH_3)_2$	93
		R = $(CH_2)_2CH_3$	95

Elemental analyses and spectral data of all products are consistent with those formulated in the Table (see experimental).

intermediate anhydride and also avoids some complications that may arise with the use of other phosphorating agents.[163,167] For instance, when diphenylphosphoryl azide is used to prepare the mixed anhydride, compounds derived via a Curtius rearrangement of the carboxylic acid azide are the usual products isolated from the reaction. Only when a good nucleophile (amine or thiol) is present in the original reaction mixture is the corresponding amide or thioate formed as the major product. Yamada has used this ready formation of the azide in a modified Curtius reaction to form urethanes and also in peptide synthesis.[167a]

The carboxylic phosphoric anhydride is rather labile to heat and base and is prone to disproportionate[168] according to the following equation.



$$2\ (R'O)_2\overset{\overset{O}{\|}}{P}\text{-}O\text{-}\overset{\overset{O}{\|}}{C}\text{-}R \ = \ (RCO)_2O \ + \ [(R'O)_2PO]_2O$$

Because of this thermal instability, the ensuing last step requires an appropriate thiolate counter-ion that brings the reaction to completion with high efficiency. Among several common cations which we tested, such as sodium and potassium, we found that thallium(I) was the most satisfactory, because of the ease of preparation and the reasonable solubility in aprotic solvents of its crystalline thiolate salts. Thus, we prepared the yellow thallium(I) salts of primary, secondary, and tertiary alkanethiols by reacting thallium(I) ethoxide with the thiols in benzene at room temperature. The thiolate salts precipitated from the benzene and were isolated in excellent yields by filtration.

Overnight stirring at room temperature of a mixture of the carboxylic phosphoric anhydride and a thallium(I) thiolate produced the corresponding, very clean, thiol ester. This method is applicable to even a reactive thiol ester such as pyridine-2-thiol (entry 2) and appears in some cases to supersede the methods employed previously because of its simple workup procedure. Pyridine-2-thiol esters have previously been prepared either *via* the acid chloride or by means of dicyclohexylcarbodiimide,[107a,b] and later by Mukaiyama *et al.* and by other groups, using triphenylphosphine and the corresponding disulphide. This latter procedure very often involves a tedious workup in order to separate the pure product from the triphenylphosphine oxide that forms concomitantly. Needless to say, in the case of a hydroxy carboxylic acid, the selectivity of the new method allows the hydroxy group of the resulting alkanethiol ester to be operated upon, followed by further conversion of the carboxy group. Of course, in cases where the acid chloride is available, and thus the selective activation of the carboxy group is not demanded, the reaction of the thallium(I) thiolate directly with the acid chloride (see Part I, Chapter 7) is the preferred method of preparing the thiol ester.

The mild, selective synthesis of thiol esters, developed to meet the demand which originated in the macrolide synthesis, has been successfully applied to many compounds including natural products, such as cytochalacins and zearalenone.

CHAPTER 2

NEW ORGANOCUPRATE REAGENTS

A) INTRODUCTION

Organocuprates were first discovered in 1936 by H. Gilman[169] when he observed that if a second equivalent of methyllithium was added to a suspension of methylcopper, then the yellow precipitate of the latter species dissolved to give a tan solution.

$$2\ LiCH_3 + CuI \longrightarrow LiCu(CH_3)_2 + LiI$$

As work in this area of chemistry progressed, three main classes of organocuprates were developed: (1) homocuprates [$LiCuR_2$], (2) mixed homocuprates [LiCuRR'] and (3) heterocuprates [LiCuRHet]. The actual structure of these compounds is not yet known, but they are usually notated as above on the basis of stoichiometry and convenience.

There are three general methods for the preparation of homocuprates.

1) $2\ LiR + CuX \longrightarrow LiCuR_2 + LiX$

2) $LiR + CuR \longrightarrow LiCuR_2$

3) $2\ LiR + L\text{-}CuX \longrightarrow LiCuR_2\text{-}L$ L = ligand

The use of a complexing ligand such as tributylphosphine both stabilizes and solubilizes the resulting homocuprate.

This third method allows the preparation of cuprates with R consisting of a secondary or tertiary alkyl group even in cases where the former two methods fail.

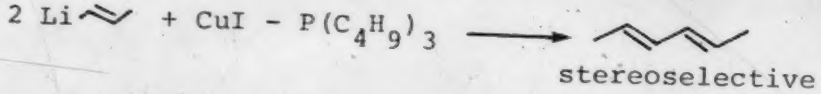
In the mid-1960's organocuprates became of increasing interest as their synthetic utility was developed. Some of the major applications of homocuprates to organic synthesis are outlined on the following few pages.

Coupling Reactions:[170]

$$LiCuR_2 \xrightarrow{[O]} R\text{-}R$$

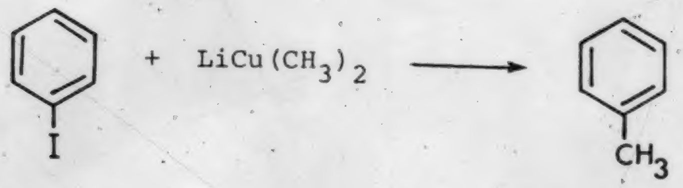
The oxidizing agent is usually oxygen, copper(II) salts or nitrobenzene. This reaction is a useful compliment to the Wurtz coupling of alkyl halides. Two examples of this coupling reaction are given below.

$$2\ LiC_4H_9 + CuI - P(C_4H_9)_3 \longrightarrow C_8H_{18}$$

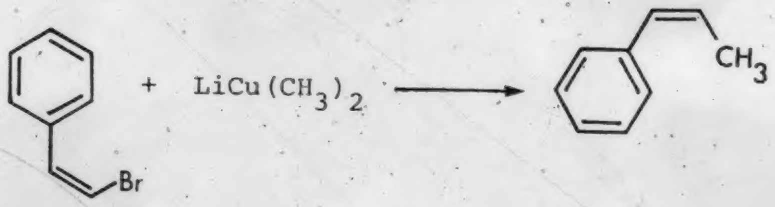

stereoselective

Reaction with Aryl, Alkyl and Acyl Halides:

This reaction is superior to that of organocopper(I) compounds (CuR) with halides. However, the disadvantage of the reaction is that a five-fold excess of the cuprate is usually required for complete reaction. Saturated halides are more reactive than aryl halides. In addition, sulphonate esters also react to produce the coupled products.

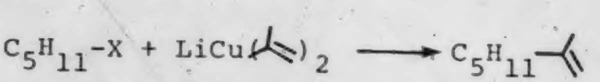


ref 171



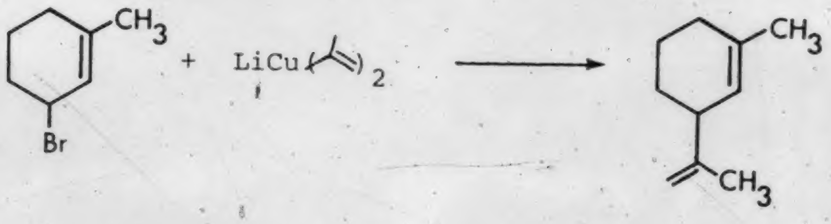
ref 172

$$C_{10}H_{21}\text{-}I + LiCu(CH_3)_2 \longrightarrow C_{11}H_{24}$$

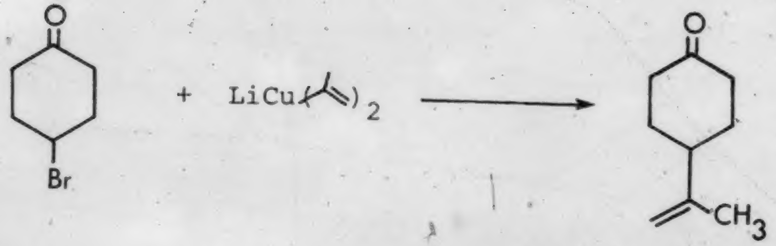


X = I,Br,Cl,OTs

Other features of this coupling reaction are that the cuprate usually reacts with allylic halides via an S_N2 mechanism rather than by the alternative S_N2' pathway, and that carbonyl protection is often not required in a competition reaction because of the high relative selectivity of the cuprate. Lithium dialkyl and diphenylcuprates also react cleanly and under mild conditions with various carboxylic acid chlorides to give the corresponding ketones in good yield.[175]



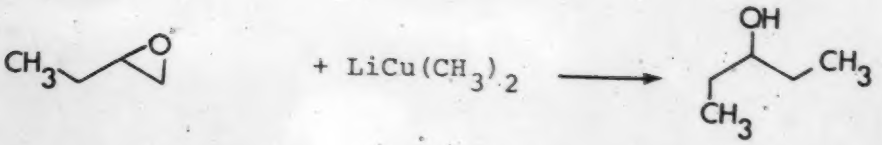
ref 172, 173



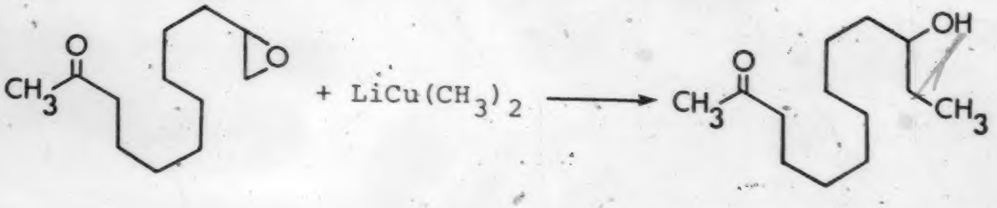
ref 174

Reaction with Epoxides:

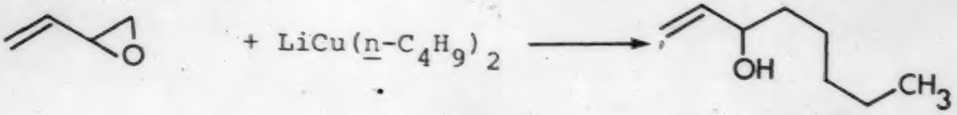
Organocuprates react more efficiently than organolithium compounds with oxiranes to give secondary alcohols via a regiospecific nucleophilic opening of the oxirane ring. Again because of the high relative selectivity of the cuprate, carbonyl protection is not always necessary. Allylic epoxides occasionally undergo 1,4 addition giving the E-allylic alcohol as the major product. However, this opening is dependent on the geometry of the substrate, and usually 1,2 addition predominates (see Part I, Chapter 5).


CH3
+ LiCu(CH3)2
OH
CH3
CH3

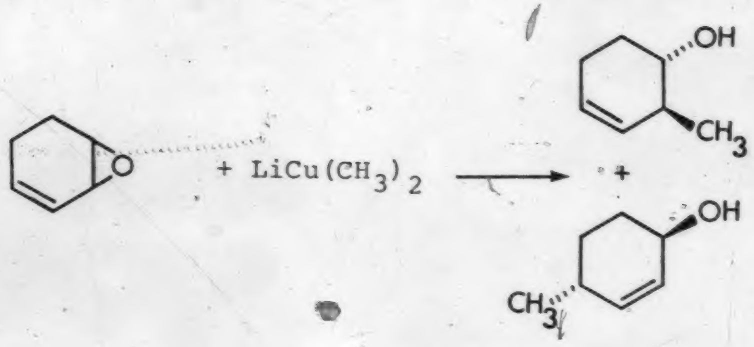
ref 127c


O
CH3
+ LiCu(CH3)2
O
CH3
OH
CH3

ref 127c


+ LiCu(n-C4H9)2
OH
CH3

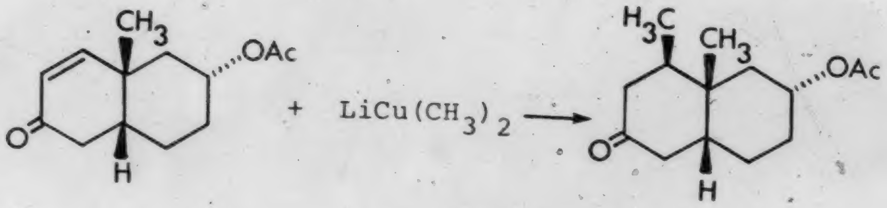
ref 128a


+ LiCu(CH3)2
OH
CH3
+
OH
CH3

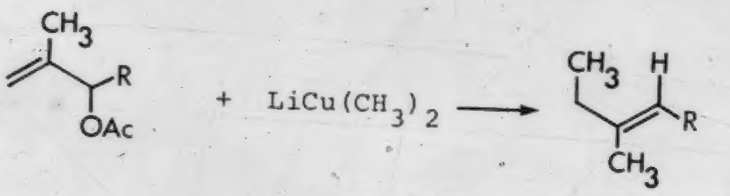
ref 129

Reactions with Conjugated Enones:

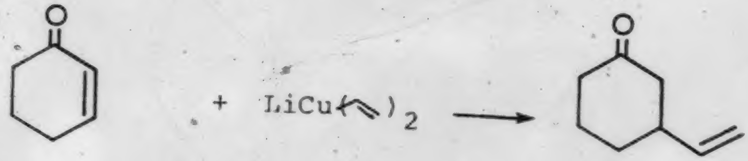
Organocuprate reagents add to α,β-unsaturated ketones and esters, and to allylic acetates in a 1,4 fashion. This reaction has been used extensively in organic synthesis, especially in cases where stereoselectivity is required. Several examples are given below.


CH3
OAc
O
H
+ LiCu(CH3)2
H3C
CH3
OAc
O
H

ref 176


CH3
R
OAc
+ LiCu(CH3)2
CH3
H
R
CH3

ref 177



ref 178

The second step in the development of organocuprates was the preparation of mixed homocuprates of the form LiCuRR', which would allow specific transfer of one of the R groups. If the cuprate $(CuRR')^-$ is viewed to be an ion composed of a cation (copper) and two anions (R and R') with a net charge of minus one, then it has been found that the group which is not transferred is the one which can form the more stable anion. Thus, the best choices for a non-transferring group would therefore include alkynyl and cyano groups, since they form stable anions. For example, if R is an alkyl group and R' is cyanide, the less stable alkyl anion is transferred. Although such groups (alkynyl, cyanide) appear to offer the greatest selectivity, there is often a drawback with the mixed cuprates since the reactivity of the second (transferable) organic group in the cuprate is significantly decreased by inclusion in the complex, relative to that which would be expected from the corresponding symmetrical homocuprate. The selectivity of transfer was found to be the same for reactions of the mixed cuprate with both halides and enones.

The reason for developing these mixed cuprates was based on the limitations of the homocuprates. One limitation is the need for a three to five fold excess of the cuprate in order to obtain complete conversion of the substrate. A second disadvantage of the procedure is reflected in the stoichiometry of the reaction i.e., only one of the two alkyl groups of the cuprate is normally converted to the product; the second is usually lost to thermal decomposition of the resulting alkylcopper(I) compound formed in the reaction. Another reason for the development of the mixed cuprate was the high thermal instability of secondary and tertiary dialkylcuprates which made them difficult to use.

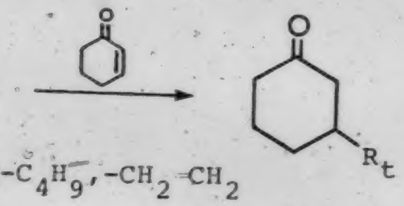
Several types of mixed cuprates have been developed. The first mixed cuprates were of the form LiCuRR', where the R group was alkyl or alkenyl, and R' was alkynyl.[179,180] Corey and Beames[181] used the following synthetic scheme to prepare a mixed cuprate.

$$CuR_r + LiR_t \longrightarrow LiCuR_rR_t$$

R_r = residual R group

R_t = transferring R group

e.g. $C_3H_7-C\equiv C-Cu + R_tLi$



$R_t = -C_4H_9$, tert-C_4H_9, $-CH_2{=}CH_2$

An extension of this idea was reported by Levisalles *et al.*[182] In their cuprate the residual group was a cyano function, which is isoelectronic with the alkynyl groups used by Corey. This cyanocuprate is reported to be as good as, if not better than, the homocuprates in substitution reaction with halides, and in 1,4 additions to α,β-unsaturated carbonyl compounds.

The next modification of the mixed cuprate was the development of a cuprate with a heteroatom group bound to copper in place of the alkynyl or cyano group. The heteroatom functions included alkoxy, aryloxy. alkylthio, arylthio and dialkylamine groups.[183] The preparation of these heterocuprates is outlined in the following scheme.

$$\mathrm{Het\text{-}H + LiBu \longrightarrow LiHet + BuH}$$

$$\mathrm{LiHet + CuI \longrightarrow CuHet + LiI}$$

$$\mathrm{CuHet + LiR \longrightarrow LiCuRHet}$$

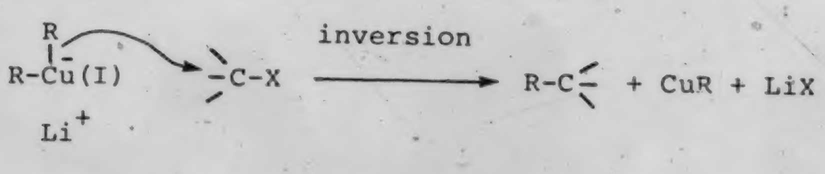
In a study by Posner *et al.*,[183] the lithium (phenylthio)alkylcuprate was found to be the most useful heterocuprate. It reacted better with carboxylic acid chlorides and α,α-dibromoketones, and equally well with alkyl halides and enones, than the corresponding homocuprates. This reagent was especially useful in accomplishing the transfer of secondary and tertiary alkyl groups. In addition, all of these reactions were achieved with only a 20-30% excess of the cuprate, which is a great improvement in the reaction efficiency.

The mechanism of the conjugate addition of organocuprates to α,β-unsaturated carbonyl compounds has been suggested by H. House[184a] to involve an electron transfer process. The reaction is believed to first involve electron transfer to the unsaturated carbonyl system to form an anion radical and an electron deficient metal cluster associated as a tight ion pair. Rebonding within this ion pair, followed by intramolecular rearrangement of an alkyl group gives the lithium enolate and an organocopper(I) compound which frequently polymerizes and precipitates out of the reaction mixture. A correlation of the polarographic reduction potentials of various α,β-unsaturated carbonyl compounds and the reactions with lithium dimethylcuprate was shown to be compatible with this mechanism.[184b]

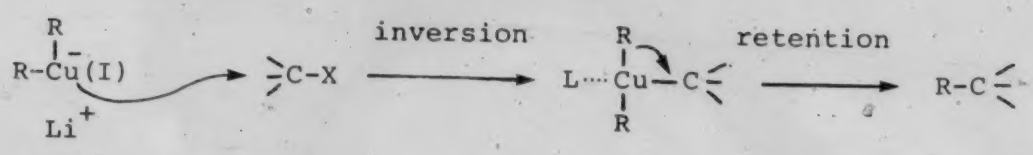
The mechanism of the reaction of organocuprates with alkyl halides and sulphonate esters is not straightforward. There have been four principle mechanistic pathways proposed for this reaction.[185b] They are summarized in Figure 9.

Figure 9: Possible Reaction Mechanisms of Organocuprates with Alkyl Halides

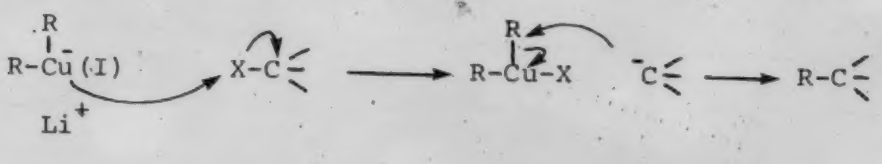
1) Nucleophilic attack by carbon


R-Cu(I) Li+
C-X
inversion
R-C + CuR + LiX

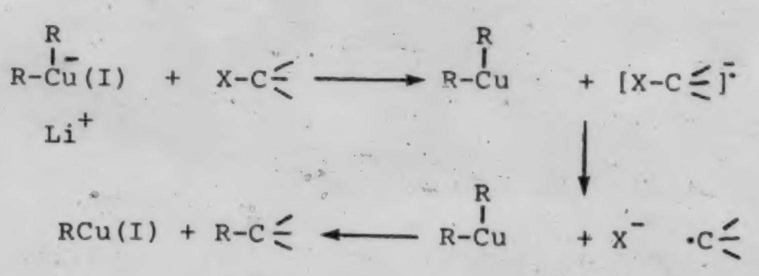
2) Nucleophilic attack by copper


R-Cu(I) Li+
C-X
inversion
L····Cu-C
retention
R-C

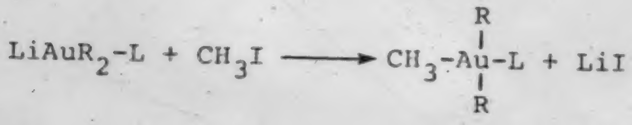
3) Nucleophilic attack by copper on the leaving group


R-Cu(I) Li+
X-C
R-Cu-X
C
R-C

4) Electron transfer process


R-Cu(I) Li+
+ X-C
R-Cu
+ [X-C]
RCu(I) + R-C
R-Cu
+ X- ·C

Johnson and Dutra[185] have made an intensive study of the reaction of lithium diorganocuprates with tosylates and have found that most secondary tosylates react with inversion of configuration, which may be accompanied by some elimination. Rate studies revealed that second order kinetics hold over a wide concentration range and only deviate at high tosylate concentrations. They eliminated the third mechanism in Figure 9 since it would likely lead to extensive or even total racemization and is not consistent with the highly stereospecific inversions observed. Their final analysis supports the second proposed mechanism. The attack by copper would explain the extraordinary nucleophilicity of the cuprates when compared with Grignard reagents or organolithium compounds. There is some support for the copper(III) intermediate suggested by Johnson and Dutra since a relatively stable trialkylgold(III) complex has been reported by Tamaki and Kochi.[186] These authors found that dialkylaurates(I) were powerful nucleophiles which reacted with iodomethane to produce a relatively stable gold(III) complex. This complex was shown to be a square



$$\mathrm{LiAuR_2{-}L + CH_3I \longrightarrow CH_3{-}\overset{\displaystyle R}{\underset{\displaystyle R}{Au}}{-}L + LiI}$$

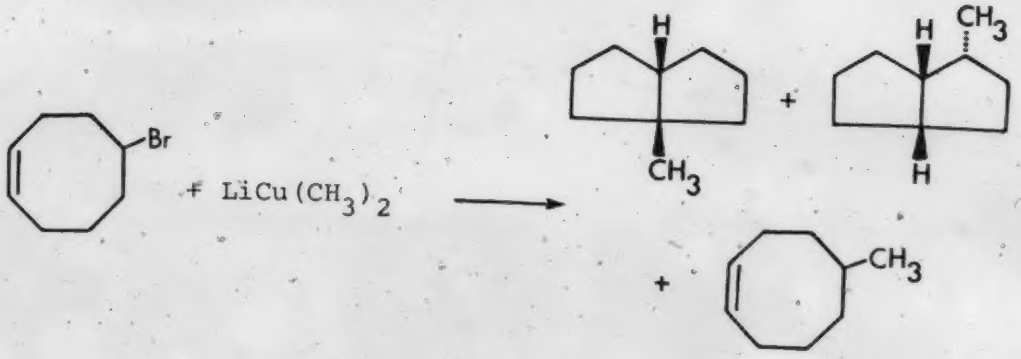
L = ligand

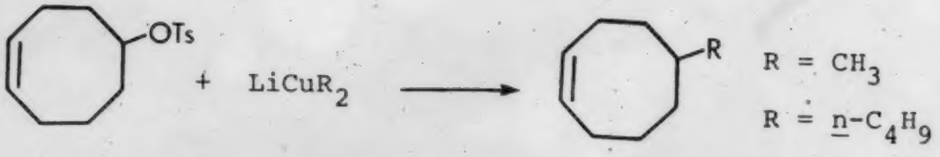
planar structure with the two alkyl groups originally present in the gold(I) complex occupying trans positions. Earlier studies had shown that gold(III) complexes decompose thermally to give alkyl coupling products and a gold(I) complex.[187]

$$R_3Au\text{-}L \xrightarrow[\Delta]{} R\text{-}R + AuR\text{-}L$$

It is reasonable to assume that copper(I) complexes might undergo similar reactions. Collapse of a copper(III) intermediate would result in the coupling of two cis ligands.

However, other studies have shown that although the mechanism suggested by Johnson and Dutra may be viable for the reaction between organocuprates and simple sulphonate esters, it does not explain all organocopper substitution reactions with alkyl-type electrophiles. Posner and Ting[188] presented evidence for the existence of a different mechanism. If a copper(III) intermediate was formed in both cases, similar product distribution should result. Since this is not the case, there is evidence for two different mechanistic pathways. They also present other cases of ethylenic participation in the reaction of organocuprates with tosylates. In addition, mechanistic studies done in this laboratory have shown that with





lithium dihydrocuprate (*vide infra*) reduction of 2-mesyloxynorboranes proceeds with inversion of configuration, whereas the reduction of the corresponding bromides takes place with retention.[134a]

Organocuprates therefore appear to react *via* several different mechanisms depending upon the substrate involved in the reaction. Whether this is indeed due to several parallel processes proceeding simultaneously or to a single as yet unexplained mechanism has not been determined.

Discussion of other reactions of cuprates and organocopper(I) species may be found in several review articles.[189]

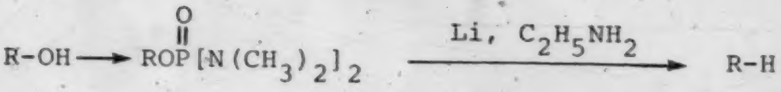
B) HYDRIDE-CONTAINING ORGANOCUPRATES

As part of our synthesis of methymycin (see Part I) it became necessary to convert an iodide or tosylate into the corresponding hydrocarbon. This problem necessitated our search for a method which would effect removal of halides and sulphonate esters, and thus indirectly hydroxy groups. There were several methods available at the time this study was begun. These included: (1) Hutchin's sodium cyanoborohydride reduction[130] which was discussed in Part I of this thesis, (2) lithium aluminum hydride reduction of halides,[190] (3) the lithium triethylborohydride reduction reported by Brown and Krishnamurthy[191] and (4) Ireland *et al.*'s reduction of the tetramethylphosphorodiamides (or diethyl phosphates) of alcohols with lithium and ethanamine.[192] The equations for these reductions are summarized below.

1) $\mathrm{R{-}X + NaBH_3CN \longrightarrow R{-}H} \quad X = OTs, I, Br$

2) $\mathrm{R{-}X + LiAlH_4 \longrightarrow R{-}H}$

3) $\mathrm{LiBH(C_2H_5)_3 + R{-}X \longrightarrow R{-}H + (C_2H_5)_3B + LiX}$

4) 

$$\mathrm{R{-}OH \longrightarrow RO\overset{O}{\overset{\|}{P}}[N(CH_3)_2]_2 \xrightarrow{Li,\ C_2H_5NH_2} R{-}H}$$

None of these reactions was, however, entirely satisfactory. We desired a method which would proceed with high efficiency, stereospecificity, operational simplicity, and under mild conditions. By analogy with the homocuprates discussed in the introduction to this chapter, it appeared that a hydride-containing cuprate would be a good choice for such a reagent. In order to synthesize the desired compound we needed a species capable of replacing the halide of a copper(I) salt by the hydride group. Lithium trimethoxyaluminum hydride[193] (LTMA) was chosen since it is soluble in aprotic organic solvents and because it has the advantage of having only one active hydrogen, and thus control of the stoichiometry of the reaction would be relatively simple.

Accordingly, it was found that the dropwise addition of two equivalents of a tetrahydrofuran solution of LTMA to a suspension of purified copper(I) iodide in tetrahydrofuran produced a thick, dark brown mixture. During the addition the mixture often became too viscous to stir and just enough tetrahydrofuran was added to allow for efficient mixing. This addition of LTMA solution with subsequent addition of a small amount of tetrahydrofuran was repeated until all of the LTMA solution had been added. It appears that forcing a gelatinous material (which we assume to be aluminum trimethoxide) out of the solution by mixing the reagents in this way is essential. Because of this obvious concentration dependence, it was found necessary that the concentration of LTMA be in the range of 0.9 to 1.1M for satisfactory results. This resulting dark brown mixture satisfied virtually all of the requirements of the desired reducing agent with a wide variety of substrates.

$$2\ \mathrm{LiAlH(OCH_3)_3} + \mathrm{CuI} \longrightarrow \text{Reagent I}$$

$$\text{R-X} + \text{Reagent I} \longrightarrow \text{R-H}$$

$$\text{X} = \text{Br, Cl, OMs, OTs}$$

Table 11 shows that the reduction proceeded with primary (entries 1-3), secondary (5-8), tertiary (9), allyl (10 and 11), vinyl (12-14), aryl (15), neopentyl bromides (16) and a cyclopropyl geminal dibromide (17). In all of these cases the yields of the reduced products were excellent and the reactions were complete in less than two hours at room temperature. We followed the reactions by gas chromatographic analysis and based the yields on relative glpc peak areas of the product and internal hydrocarbon (octane or decane) standard which were corrected for the relative sensitivity of the detector. Once conditions had been worked out for the reaction the reaction was scaled up. It proceeded just as well on a preparative (30 mM) scale. Furthermore, primary (18) and secondary (19-21) mesylates, tosylates (22) and an epoxide (23) underwent equally smooth reductive cleavage.

Table 11: Reduction with Reagent I[a]

Entry	Substrate	Product	Yield (%)	Time (hr)
1	1-bromooctane	octane	98	1.0
2	1-bromononane	nonane	98	2.0
3	1-bromononane	nonane	95[b]	2.0
4	1-chlorooctane	octane	96[c]	15
5	2-bromononane	nonane	100	1.25
6	2-bromoadamantane	adamantane	99	1.5
7	*exo*-2-bromonorbornane	norbornane	92	1.0
8	*endo*-2-bromonorbornane[d]	norbornane	93	1.0
9	1-bromoadamantane	adamantane	100	1.75
10	3-bromocyclohexene[e]	cyclohexene	99	0.5[f]
11	geranyl chloride[g]	*trans*-2,6-dimethyl-octa-2,6-diene	85	0.5[h]
12	*cis*-1-bromooct-1-ene[i]	oct-1-ene	96	2.5
13	*trans*-1-bromooct-1-ene[j]	oct-1-ene	98	2.5
14	1-bromocyclooctene[k]	cyclooctene	99	2.5
15	1-bromonaphthalene	naphthalene	100	2.0
16	1-bromo-2,2-dimethylhexane[l]	2,2-dimethylhexane	97	2.0
17	9,9-dibromobicyclo[6.1.0]nonane	bicyclo[6.1.0]nonane[m]	85[c]	1.0

Table 11: Continued

Entry	Substrate	Product	Yield (%)	Time (hr)
18	1-octanol mesylate[n]	octane	95	1.5
19	2-nonanol mesylate	nonane	99	1.0
20	*exo*-2-norbornanol mesylate[o]	norbornane	99[c]	2.0
21	*endo*-2-norbornanol mesylate[p]	norbornane	75[c]	5.0
22	cyclohexanol tosylate[q]	cyclohexane	98	1.5
23	cyclohexene oxide	cyclohexanol	100	1.5

Notes:

[a] All runs were performed on a 2.73 mM scale with 1 molar equiv of reagent which was prepared at 0° and the reaction run at room temperature. All yields are based on relative glpc peak areas, corrected for the sensitivity of the detector, using octane or decane as reference.

[b] Preparative scale (27.2 mM); product isolated.

[c] 2 molar equivalents of reagent used.

[d] J. D. Roberts, E. R. Trumbell, Jr., W. Bennett, R. Armstrong, *J. Amer. Chem. Soc.* **72**, 3116 (1950); J. D. Roberts, W. Bennett, R. Armstrong, *ibid.* **72** 3329 (1950).

[e] R. Monson, "Advanced Organic Synthesis", Academic Press, New York, N.Y., 1971, p. 48.

[f] Reaction performed at -30°.

[g] J. Calzada, J. Hooz, *Org. Syn.* **54**, 63 (1975).

Table 11: Continued

Notes: Continued

[h] Reaction performed at 0°.

[i] H. C. Brown, D. H. Bowman, S. Misumi, M. K. Unni, *J. Amer. Chem. Soc*. **89**, 4531 (1967).

[j] G. Zweifel, C. C. Whitney, *ibid*. **89**, 2753 (1967).

[k] G. Wittig, H. L. Dorsch, *Justus Liebigs Ann. Chem*. **711**, 46 (1968).

[l] B. Stephenson, G. Solladié, H. S. Mosher, *J. Amer. Chem. Soc*. **94**, 4184 (1972).

[m] E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).

[n] Methanesulphonate esters were prepared according to the procedure of R. K. Crossland and K. L. Servis, *J. Org. Chem*. **35**, 3195 (1970).

[o] Alcohol prepared according to text reference 196.

[p] Alcohol prepared according to text reference 195.

[q] 4-Toluenesulphonate esters were prepared using standard (4-toluenesulphonyl chloride/pyridine) conditions.

A chloride (4) required a longer reaction time and an excess amount of the reducing agent in order to achieve a 96% yield of product. However, even this tardy reaction is very gratifying when compared with the sodium cyanoborohydride reduction which yielded less than 2% of the corresponding hydrocarbon after treatment with four molar equivalents of the borohydride for 92 hours at room temperature.

The near quantitative reduction of the substrates was only realized when two molar equivalents of LTMA with respect to copper(I) iodide (or substrate) was used to prepare the reagent. When one equivalent of hydride was used the reduction proceeded only to an extent of 50% completion or less. We believe that this result suggests that the reducing species is a cuprate, which may be formulated as $LiCuH_2$ on the basis of its apparent stoichiometry, and that copper(I) hydride,[194] which has been reported to have some reducing power,[194b] is only partially responsible for the reaction if at all.

In order to investigate the stereochemistry of the reaction, lithium trimethoxyaluminum deuteride was used to prepare the reagent and the reaction mixture was worked up with H_2O. Interestingly the reduction of both exo- and endo-2-bromonorbornones proceeded with 100% retention, whereas the corresponding methanesulphonate esters[195,196] underwent complete inversion of stereochemistry. Careful integration of the pmr spectra of samples collected by preparative gas chromatography was used to study the stereochemistry of deuterium incorporation. These results are summarized in Table 12. For instance, the product isolated from the reduction of *endo*-2-bromonorborane was identified as the pure *endo*-*d* isomer by measuring the decrease in the intensity of the pmr signal at τ 8.87 (*endo* H) using the intensity of the bridgehead protons (τ 7.72) as a standard. While the relative intensity of the *exo* protons (τ 8.57) to the bridgehead protons remained unchanged (4:2) as in the case of norbornane, the intensity of the signal due to the *endo* protons at τ 8.87 diminished by an amount corresponding to one proton in the deuterated product. Ir spectra of the samples confirmed the *endo* and *exo* assignments of the 2-deuterionorbornanes.[197]

The stereospecificity of the reduction of (*E*)-1-bromo-oct-1-ene is interesting. First, (*E*)-1-deuteriooct-1-ene was prepared as a standard using the procedure reported by Wilke and Müller.[198]

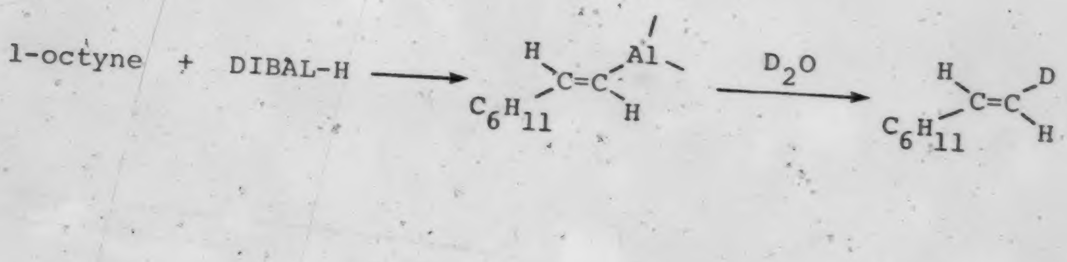


Table 12: Deuterium Incorporation into Norbornane

Compound	Relative Proton Integrations		
	Bridging & *endo*	*exo*-	Bridgehead
Norbornane	6.0	4.0	2.0
exo-2-Deuterionorbornane (*endo*-mesylate)	6.2	3.3	2.0
exo-2-Deuterionorbornane (*exo*-bromide)	6.0	3.2	2.0
endo-2-Deuterionorbornane (*exo*-mesylate)	5.3	3.8	2.0
endo-2-Deuterionorbornane (*endo*-bromide)	5.3	4.0	2.0
Integrated Region	τ 8.7-9.0	8.4-8.7	7.75-7.92

Use of the deuterated copper reagent with an H_2O workup led to no deuterium incorporation in the product, whereas an approximately 1:1 mixture of (E)- and (Z)-1-deuterio-oct-1-ene resulted upon treatment with the non-deuterated reagent and a D_2O workup. These experiments clearly show that hydrogen (or deuterium) was introduced at the workup stage with H_2O (or D_2O) serving as the proton source. Although the stereochemical integrity was lost in the reaction,[199] apparently thermally (room temperature) stable organocopper complexes were formed. This stability is not seen with the saturated substrates such as the norbornane derivatives described above where the reagent is the source of the incorporated deuterium. This is also the case with the reduction of 1-bromoadamantane; the mass spectrum of the reduction product showed high deuterium incorporation.

The above results suggest that, as with dialkylcuprates, the reaction mechanism is very complex, and that two or more different pathways are available for the reactions. This copper reagent has also recently been shown by Semmelhack and Stauffer[200] to add in a 1,4 fashion to α,β-unsaturated carbonyl systems via an electron transfer process.

The reducing reagent described above was extremely efficient but had the disadvantage that it also readily reduced carbonyl functions, and thus did not possess as wide a scope as we desired. Again by analogy with other cuprates, we felt that if we could develop a mixed cuprate (LiCuHR) containing an alkyl or alkynyl group which would not be transferred during the reaction, then perhaps the reactivity of the reagent would be lowered making it more selective.

There are several methods available for preparing copper(I) hydride,[194] but we found that the Whitesides procedure[194b] gave the best results and this procedure was used throughout our study. Polymeric copper(I) hydride was prepared by adding diisobutylaluminum hydride to a pyridine solution of purified copper(I) iodide at -50°. After 30 minutes the reaction was centrifuged to compact the product and the solvent was removed by syringe. Our modified cuprate was then prepared by reacting this copper(I) hydride with an equimolar amount of an alkyl (or alkynyl) lithium in either tetrahydrofuran or ether at -40°. The alkynyllithium solutions were prepared from the alkyne and halide-free methyllithium.

We used 2-bromononane as a substrate in order to examine the reaction variables that influence the reactivity of the copper complexes and the yield of the product (nonane contaminated with a minute (3-4%) amount of nonene). These results are summarized in Table 13. The first four entries show that four molar equivalents of cuprate is

Table 13: Reduction of 2-Bromononane with LiCuHR[a]

Entry	LiCuHR R	Molar Ratio Reagent/Substrate	Solvent	Reaction Time (hr)	Temperature	Yield (%)
1	$\underline{n}$-C_4H_9	1:1	ether	1 and 3	25°	15 and 15
2	$\underline{n}$-C_4H_9	2:1	ether	1 and 3	25°	26 and 26
3	$\underline{n}$-C_4H_9	3:1	ether	1 and 3	25°	58 and 70
4	$\underline{n}$-C_4H_9	4:1	ether	1	25°	100
5	$\underline{tert}$-C_4H_9	4:1	ether	3 and 12	25°	35 and 80
6	$\underline{iso}$-C_3H_7	4:1	ether	3	25°	25
7	$C{\equiv}C$-$\underline{n}$-C_3H_7	4:1	ether	4	0°	3-5
8	$C{\equiv}C$-$\underline{n}$-C_3H_7	4:1	ether	4	25°	40
9	$C{\equiv}C$-$\underline{n}$-C_3H_7	4:1	tetrahydrofuran	4	25°	0
10	$\underline{n}$-C_4H_9	4:1	ether	1	0°	70
11	$\underline{n}$-C_4H_9	4:1	tetrahydrofuran	1	0°	~0
12	$\underline{n}$-C_4H_9	4:1	tetrahydrofuran	3	25°	10

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[a] All runs were performed on a 6 mM scale with respect to the reagent. The yields are based on relative glpc peak areas, corrected for the sensitivity of the detector, using decane as reference.

required to complete the reduction in a short reaction time. Of several complexes differing in the residual group, the reaction proceeds most satisfactorily with $LiCuH(\underline{n}\text{-}C_4H_9)$,* and diethyl ether is definitely superior to tetrahydrofuran as a solvent. A simple kinetic study of the reduction of 2-bromononane with $LiCuH(\underline{n}\text{-}C_4H_9)$ over a temperature range of -40 to 20° showed that the reduction followed roughly second order kinetics. We believe that the smooth increase in rate as the temperature is raised indicates at least that the reagent is stable and undergoes no dramatic change in structure and degree of aggregation in solution over a wide range of temperature. Figure 10 shows this kinetic data.

From the information in Table 13 it was apparent that four molar equivalents of $LiCuH(\underline{n}\text{-}C_4H_9)$ in ether at room temperature was a satisfactory reduction medium and these conditions were applied to a variety of substrates. Table 14 summarizes the results obtained with representative samples. Reduction of primary, secondary, and tertiary halides and mesylates (or tosylates) was found to proceed well. It is interesting that the homoallylic tosylate

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*As noted earlier, this formula merely indicates the ratio of each reagent used to prepare the reducing species.

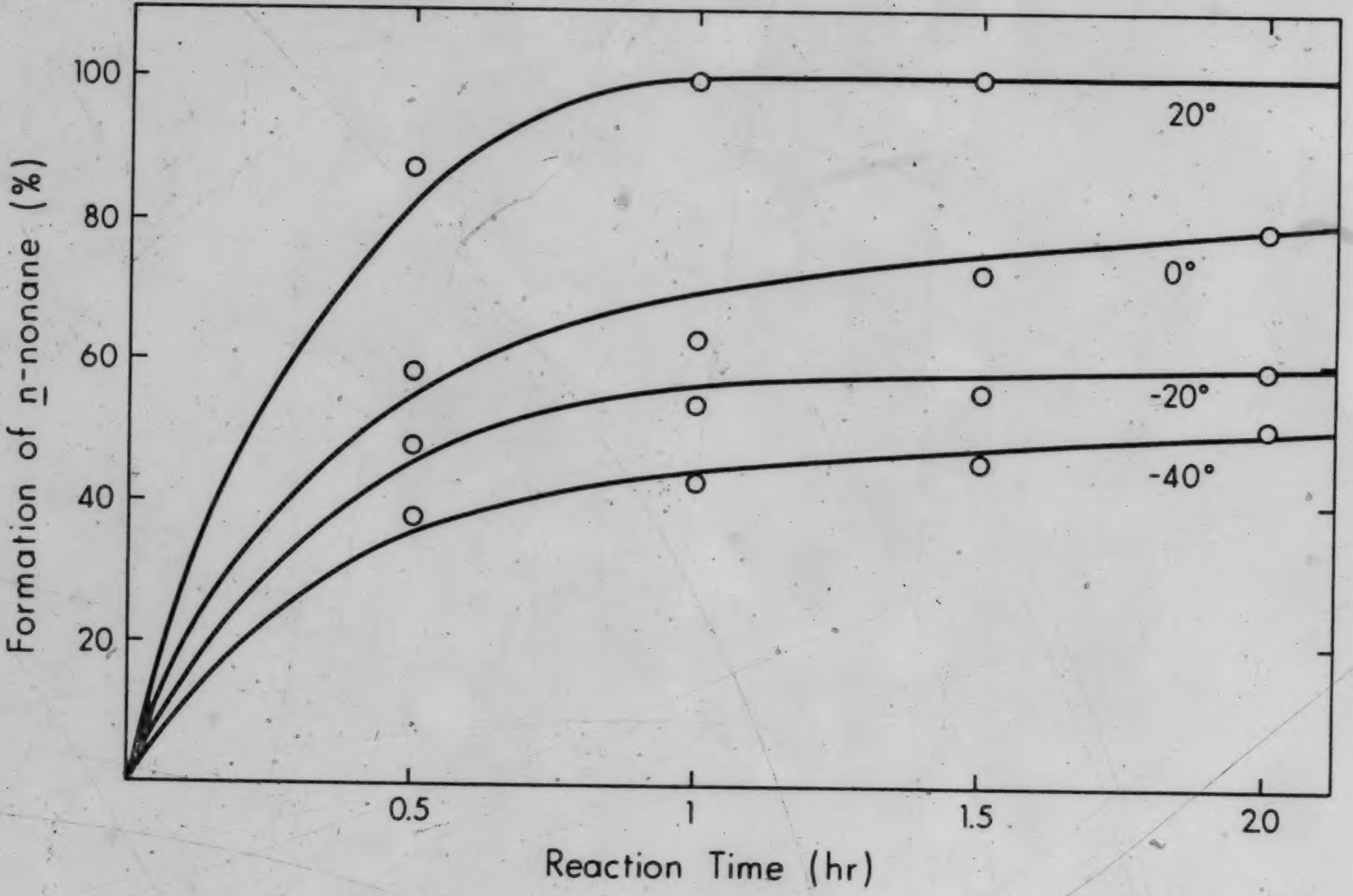


Figure 10: Approximate Rates of Reduction of 2-Bromononane with LiCuH($\underline{n}$-C_4H_9) at Various Temperatures. Reagent, 0.3$\underline{M}$; Substrate, 0.075$\underline{M}$.

Table 14: Reduction with 4 Molar Equivalents of LiCuH(n-C_4H_9) in Ether at 25°[a]

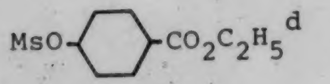
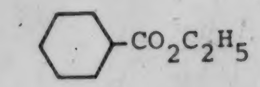
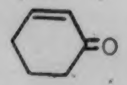
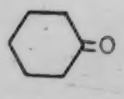
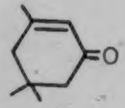
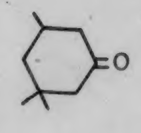
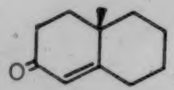
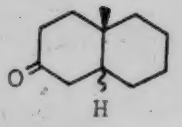
Entry	Substrate	Product	Yield	Time (hr)
1	*exo*-2-bromonorbornane	norbornane	85	1
2	1-bromoadamantane	adamantane	70	2
3	1-bromonaphthalene	naphthalene	95	3
4	octanol tosylate	octane	80	2.5
5	cyclohexanol tosylate	cyclohexane	80	2.5
6	3-cyclohexen-1-ol tosylate[b]	cyclohexene (no diene)	75	2
7	2-octanol mesylate	octane	~100	1
8	ethyl octanoate	octanol	2-3	2
9	heptyl acetate	heptanol	20	2
10	heptaldehyde[c]	heptanol	100	0.5
11	cyclohexanone[c]	cyclohexanol	100	0.5
12	2-bromononane and ethyl octanoate	nonane and ethyl octanoate	95 100	2
13	ethyl 12-mesyloxy-stearate	ethyl stearate	100 90 (isolated)	2
14	 MsO-$CO_2C_2H_5$[d]	 $CO_2C_2H_5$	100	0.5

Table 14: continued

Entry	Substrate	Product	Yield	Time (hr)
15	ethyl 12-bromostearate[e]	ethyl stearate	85 (isolated)	2
16			95	0.5 (-40°)
17			95	0.5 (-40°)
18	 f	cis/trans 7:3[g] 	85 (isolated)[h]	2 (-40°)

Notes:

[a] The conditions are the same as in Table 13. Naphthalene was used as a glpc reference in the case of the enone reductions.

[b] The alcohol was prepared by a standard lithium aluminum hydride reduction of the corresponding epoxide. For the epoxide preparation see: J. K. Crandall, D. B. Banks, R. A. Colyer, R. J. Watkins, J. P. Arrington, J. Org. Chem. 33, 423 (1968).

[c] cf. L. T. Scott, W. D. Cotton, J. Chem. Soc., Chem. Commun., 320 (1973); E. J. Corey, I. Kuwajima, J. Amer. Chem. Soc. 92, 395 (1970).

Table 14: Continued

Notes: Continued

[d] See text reference 131.

[e] Prepared from the corresponding hydroxy compound. See: J. Hooz, S. S. H. Gilani, *Can. J. Chem.* **46**, 86 (1968)

[f] C. H. Heathcock, J. E. Ellis, J. E. Murry, A. Coppolino, *Tetrahedron Lett.*, 4995 (1971).

[g] *Cis*: R. L. Augustine, A. D. Broom, *J. Org. Chem.* 25, 802 (1960). Hydrogenation over Pd/C performed in this laboratory provided a 93:7 mixture of the *cis* and *trans* compounds.

[h] 15% of the starting material recovered.

(entry 6) provided the corresponding alkene without complication. This result is in contrast with the report of Posner and Ting[188] concerning ethylenic participation described in the introduction to this chapter. An aldehyde and a ketone (vide infra) were readily reduced to the corresponding hydroxy compounds with no incorporation of the n-C_4H_9 group which was rather surprising. The ester group resisted reduction (entries 8 and 9) and in fact survived completely in both inter- and intramolecular competition experiments (entries 12-15).

Our goal has thus been achieved to prepare a mild, high yield, stereospecific reducing agent for halides and sulphonate esters.

We also investigated a rather interesting extension of this reagent. Although aldehydic and ketonic compounds are readily reduced with the cuprate complex, the carbonyl groups may survive as enolates if 1,4- rather than 1,2-addition to the α,β-unsaturated carbonyl system occurs. Because of the higher susceptibility of the enone system to this reduction than halo and mesyloxy groups, the reaction is complete within thirty minutes at -40° with LiCuH(n-C_4H_9) in ether. The resulting enolate then could be used directly for further reactions such as alkylation and Michael addition.[201] House[202] has shown that in some cases at least that reduction of an enone system with a cuprate is a result of the thermal decomposition of the reagent to form copper(I) hydride derivatives. There is thus some discrepancy concerning the actual reducing species that effects the reduction of enone systems. This aspect of the organocuprate is currently being investigated.

CHAPTER 3

EXPERIMENTAL

General: See page 142.

Diethyl Phosphorochloridate

This reaction was carried out according to the procedure reported by Steinberg.[203]

Triethylamine (3.2 ml, 2.32 g, 23 mM) was slowly added to a cold (0°), stirred mixture of diethyl phosphite (27.6 g, 200 mM) and carbon tetrachloride (35 ml, 61 g, 400 mM). After 15 min at 0° the reaction mixture was allowed to warm to room temperature. Stirring was continued for 3 hr before the mixture was filtered and the filtrate evaporated. The residue was distilled to give 28 g (81%) of the chloridate as a colourless liquid (bp 64°, 5 mm).

Thallium(I) 2-Methyl-2-propanethiolate

2-Methyl-2-propanethiol (1.98 g, 22 mM) was added dropwise over 5 min to a stirred solution of thallium(I) ethoxide (5.0 g, 20 mM) in anhydrous benzene (20 ml). After 15 min the precipitate was filtered under argon and washed thoroughly with anhydrous pentane (3 x 10 ml) to give 5.6 g (95%) of thallium(I) 2-methyl-2-propanethiolate as bright yellow crystals (mp 170-175°, decomp).

The same procedure was used to prepare the thallium(I) salts of pyridine-2-thiol, propanethiol, 2-propanethiol, and benzenethiol. These thiolates were also bright yellow and were prepared in yields of 85 to 95%.

S-tert-Butyl Cyclohexanemethanethioate

Diethyl phosphorochloridate (1.73 g, 10 mM) in anhydrous tetrahydrofuran (5 ml) was added dropwise to a solution of cyclohexanecarboxylic acid (1.28 g, 10 mM) and triethylamine (1.01 g, 10 mM) in anhydrous tetrahydrofuran (25 ml). The mixture was stirred at room temperature for 3 hr, and the precipitated triethylamine hydrochloride was removed by filtration and washed with tetrahydrofuran (10 ml). To the combined filtrate and washing was added thallium(I) 2-methyl-2-propanethiolate (3.22 g, 11 mM), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was filtered through Celite and the filter pad washed with ether (2 x 10 ml). The combined filtrate was evaporated, and the residue dissolved in ether (50 ml). The ether solution was washed with aqueous saturated sodium bicarbonate (10 ml), aqueous saturated sodium chloride (2 x 10 ml), dried ($MgSO_4$) and evaporated. The residue was distilled to give 1.87 g (94%) of colourless S-tert-butyl cyclohexanemethanethioate (bp 58-61°, 0.05 mm).

ir ($CHCl_3$): 1680 (s)

pmr (CCl_4); τ 7.6 (m, 1H), 7.9-8.8 (m, 10H), 8.57 (s, 9H)

mass spectrum: calcd for $C_{11}H_{20}O^{32}S$: m/e = 200.12349

measured: m/e = 200.12323

elemental analysis: calcd for $C_{11}H_{20}OS$: C 65.95; H 10.06; S 16.00

found: C 66.19; H 10.12; S 16.21

The above procedure was used to prepare the other thiol esters in Table 10. The physical properties of these products are given below.

S-2-Propyl Cyclohexanemethanethioate

bp: 55°, 0.3 mm

ir ($CHCl_3$): 1685 (s)

pmr ($CDCl_3$): τ 6.45 (sept, J = 7, 1H), 7.6 (m, 1H)
8.0-8.8 (m, 10H), 8.72 (d, J = 7, 6H),

mass spectrum: 186 (P)

elemental analysis: calcd for $C_{10}H_{18}OS$: C 64.52, H 9.68, O 8.6, S 17.20

found: C 64.59, H 9.74, O 8.86, S 17.27

S-Propyl Cyclohexanemethanethioate

bp: 61-63°, 0.4 mm

ir ($CHCl_3$): 1685 (s)

pmr ($CDCl_3$): τ 7.10 (t, J = 6.5, 2H), 7.6 (m, 1H),
8.0-8.8 (m, 12H), 9.03 (t, J = 6.5, 3H)

mass spectrum: 186 (P)

elemental analysis: calcd for $C_{10}H_{18}OS$: C 64.52, H 9.68,
O 8.60, S 17.20
found: C 64.31, H 9.50,
O 8.45, S 16.91

S-Phenyl Cyclohexanemethanethioate

bp: 180-110°, 0.1 mm

ir ($CHCl_3$): 1700 (s)

pmr ($CDCl_3$): τ 2.58 (s, 5H), 7.5 (m, 1H), 7.8-8.8
(m, 10H)

mass spectrum: 220 (P)

elemental analysis: calcd for $C_{13}H_{16}OS$: C 70.91, H 7.27
O 7.27, S 14.55
found: C 70.80, H 7.33,
O 7.53, S 14.73

S-2-Pyridine Cyclohexanemethanethioate

bp: prepared by tlc

ir ($CHCl_3$): 1705 (s)

pmr ($CDCl_3$): τ 1.3 (m, 1H), 2.3-3.1 (m, 3H), 7.35 (m, 1H), 7.7-9.0 (m, 10H)

mass spectrum: calcd for $C_{12}H_{15}NO^{32}S$: m/e = 221.08744

measured: m/e = 221.08738

S-tert-Butyl Thiol Ester of Cholic Acid

mp: 164-165°

ir ($CHCl_3$): 3620, 3600-3300, 1680

pmr ($CDCl_3$): τ 8.61 (s, 9H), 9.05 (d, J = 6, 3H), 9.1 (s, 3H), 9.32 (s, 3H)

mass spectrum: calcd for $C_{28}H_{44}O_2{}^{32}S$ (P-2OH):

m/e = 444.30620

measured: m/e = 444.30562

elemental analysis: calcd for $C_{28}H_{48}O_4S$: C 69.97, H 10.07

O 13.32, S 6.67

found: C 69.21, H 9.94,

O 14.10, S 6.83

S-2-Propyl Thiol Ester of Cholic Acid

mp: 142-143°

ir ($CHCl_3$): 3620, 3300-3500, 1680

pmr ($CDCl_3$): τ 6.5 (sept, J = 7, 1H), 8.7 (d, J = 7, 6H), 9.1 (s, 3H), 9.32 (s, 3H)

mass spectrum: 466 (P)

elemental analysis: calcd for $C_{27}H_{46}O_4S$: C 69.50, H 9.93
O 13.72, S 6.87
found: C 69.20, H 9.94,
O 13.57, S 6.97

S-Propyl Thiol Ester of Cholic Acid

mp: 146-148°

ir ($CHCl_3$): 3610, 3300-3500, 1680

pmr ($CDCl_3$): τ 7.1 (t, J = 7, 2*H*), 8.9 (t, J = 7, 3*H*), 9.05 (d, J = 6.5, 3*H*), 9.1 (s, 3*H*), 9.32 (s, 3*H*)

mass spectrum: 466 (P)

elemental analysis: calcd for $C_{26}H_{44}O_4S$: C 69.50, H 9.93
O 13.72, S 6.87
found: C 69.39, H 9.93
O 13.79, S 7.01

S-*tert*-Butyl 12-Hydroxyoctadecanethioate

mp: 39-40°

ir ($CHCl_3$): 3620, 1675

pmr ($CDCl_3$): τ 6.4 (bs, 1*H*), 7.6 (t, J = 7, 2*H*), 8.2-8.8 (38*H*) 8.5 (s, 9*H*), 8.7 (bs), 9.1 (t, J = 7, 3*H*)

mass spectrum: calcd for $C_{18}H_{35}O_2$ [P-SC$(CH_3)_3$]:
m/*e* = 283.26370

measured: *m*/*e* = 283.26251

S-*tert*-Butyl Thiol Ester of *N*-Carbobenzyloxy-*L*-Proline

bp: Prepared by tlc

ir ($CHCl_3$): 1700, 1680

pmr ($CDCl_3$): τ 2.70 (s, 5*H*), 5.0 (s, 2*H*), 4.5 (m, 1*H*),
6.4 (m, 2*H*), 7.75-8.3 (m, 4*H*), 8.6 (s, 9*H*)

mass spectrum: calcd for $C_{17}H_{23}NO_3{}^{32}S$: *m*/*e* = 321.13986
measured: *m*/*e* = 321.13902

elemental analysis: calcd for $C_{17}H_{23}NO_3S$: C 63.52, H 7.21,
N 4.36, S 9.98
found: C 63.15, H 7.26,
N 4.32, S 9.90

S-2-Propyl Thiol Ester of *N*-Carbobenzyloxy-*L*-Proline

bp: 110°, 0.5 mm

ir ($CHCl_3$): 1740, 1660

pmr ($CDCl_3$): τ 2.7 (s, 5*H*), 4.85 (s, 2*H*), 5.55 (m, 1*H*),
6.45 (m, 3*H*), 7.95 (m, 4*H*), 8.75 (d, J = 7,
6*H*)

mass spectrum: 307 (P)

elemental analysis: calcd for $C_{16}H_{21}NO_3S$: C 62.54, H 6.84,
N 4.56, O 15.64,
S 10.42

found: C 62.19, H 6.83,
N 4.50, O 16.15,
S 10.43

S-Propyl Thiol Ester of N-Carbobenzyloxy-L-Proline

bp: 110°, 0.5 mm

ir ($CHCl_3$): 1720, 1660

pmr ($CDCl_3$): τ 2.65 (s, 5H), 4.85 (s, 2H), 5.5 (m, 1H),
6.4 (ct, J = 7, 2H), 7.15 (t, J = 6.5, 2H),
7.8-8.7 (m, 6H), 9.1 (t, J = 6.5, 3H)

mass spectrum: 307 (P)

elemental analysis: calcd for $C_{16}H_{21}NO_3S$: C 62.54, H 6.84,
N 4.56, O 15.64,
S 10.42

found: C 62.17, H 6.89,
N 4.22, O 16.22,
S 10.32

The following two experimental procedures are representative of the methods used for the reductions summarized in Tables 11 and, 13 and 14, respectively. References for the preparation of non-commercially available substrates are indicated in the above tables.

Reduction of 1-Bromononane with the Dihydrocuprate

The procedure reported by Brown et al.[193] was used to prepare lithium trimethoxyaluminum hydride. Copper(I) iodide was purified according to the method of Kaufmann and Teter,[158] and is described in Part I of this thesis.

Anhydrous methanol (6.63 ml, 5.25 g, 163.5 mM) was added dropwise with vigorous stirring to a cold (0°) tetrahydrofuran solution (1.09M, 50 ml, 54.5 mM) of lithium aluminum hydride over 30 min. After the addition was completed, the clear colourless solution was stirred a further 20 min at 0°.

The freshly prepared LTMA solution was added dropwise to an ice-cooled slurry of purified copper(I) iodide (5.18 g, 27.2 mM) in anhydrous tetrahydrofuran (10 ml). With the first few drops of the hydride solution, the suspension became gelatinous and sufficient tetrahydrofuran (5-10 ml) was added to facilitate stirring. This sequence was continued until all of the hydride solution had been added; the addition takes approximately 30 min. It was necessary to add a total of 150 ml of tetrahydrofuran. After the addition was completed, the resulting brown mixture was stirred 30 min at 0°, and then 1-bromononane (6.54 g, 27.2 mM) was added all at once. After 15 min the cooling bath was removed, and the mixture vigorously stirred for 2 hr at room temperature. On several occasions a gel formed and enough tetrahydrofuran was added to allow efficent stirring. Methanol (20 ml) was added slowly, the mixture diluted with ether (250 ml) and filtered through Celite. The solvent was evaporated and the residue dissolved in ether (250 ml) and washed with aqueous saturated ammonium chloride (3 x 25 ml). The organic phase was dried ($MgSO_4$) and evaporated. The residue was distilled to give 3.3 g (95%) of pure nonane (bp 150-151°).

Reduction of Octanol Tosylate with the Mixed Cuprate

The Whiteside's procedure[194b] was used for the preparation of the copper(I) hydride complex.

A benzene solution (1.2M, 5 ml, 6 mM) of diisobutylaluminum hydride was added over 1-2 min to a cold (-40°) solution of purified copper(I) iodide (1.14 g, 6 mM) in anhydrous pyridine (10 ml). The resulting brown solution was immediately cooled to -50° and stirred vigorously for 30 min. Cold (-70°) ether (20 ml) was added to precipitate the copper(I) hydride. The slurry was compacted by centrifugation at -70°, and the supernatant liquid was removed by syringe. The copper(I) hydride complex was washed in this manner with cold ether (3 x 20 ml) to give a medium brown solid.

The copper(I) hydride complex was slurried with cold ether (20 ml) and the suspension maintained at -40°. With vigorous stirring a hexane solution (1.6M, 3.75 ml, 6.0 mM) of butyllithium was added over 5 min. The resulting dark brown solution (reagent partially insoluble) was stirred for 10 min before octanol tosylate (427 mg, 1.5 mM) was added. The cooling bath was removed and stirring was continued for 2.5 hr at room temperature. The reaction was poured into aqueous saturated ammonium chloride (10 ml) the ether layer decanted and the aqueous phase extracted with ether (2 x 25 ml). The ether was dried ($MgSO_4$) and evaporated. The residue was molecularly distilled to give 137 mg (80%) of colourless octane.

The same procedure was applied to the reduction of the enones in Table 14 except that the reaction temperature was maintained at -40°.

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